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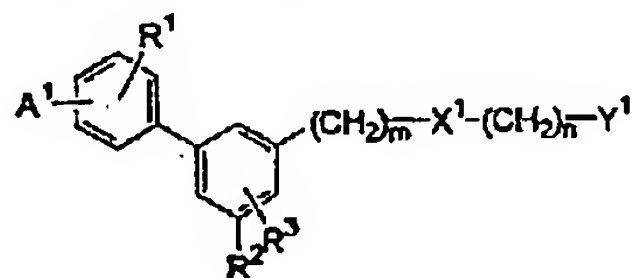
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(54) 【発明の名称】 ビフェニルアミジン誘導体

(57) 【要約】 (修正有)

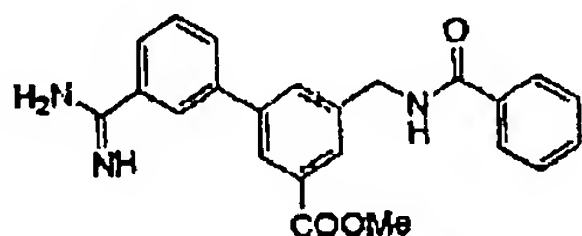
【課題】 臨床応用可能な F X a 抑制剤となり得る新規化合物を提供することである。

【解決手段】 下記式 (1)



(1)

具体的には、例えば



で表されるビフェニルアミジン誘導体またはその薬学的に許容される塩。

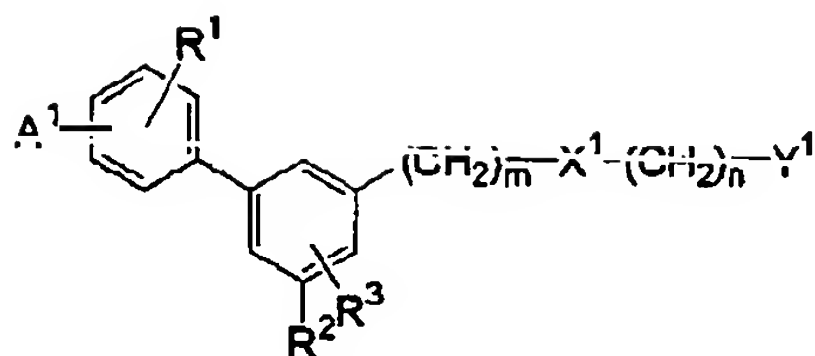
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【特許請求の範囲】

【請求項1】 下記式(1)



(1)

〔式(1)中、

A¹はアミノ基を表し、

R¹は、水素原子、フッ素原子、塩素原子、臭素原子、水酸基、アミノ基、ニトロ基、C₁~₁₀アルキル基、または、C₁~₁₀アルコキシ基を表し、

R²は、フッ素原子、塩素原子、臭素原子、水酸基、アミノ基、C₁~₁₀アルコキシ基、カルボキシル基、C₁~₁₀アルコキシカルボニル基、アリールオキシカルボニル基、アラルコキシカルボニル基、カルバモイル基（カルバモイル基を構成する窒素原子は、モノーもしくは、ジ-C₁~₁₀アルキル基で置換されていても良く、またはアミノ酸の窒素原子でもよい。）、C₁~₁₀アルキルカルボニル基、C₁~₁₀アルキルスルフェニル基、C₁~₁₀アルキルスルフィニル基、C₁~₁₀アルキルスルホニル基、モノーもしくはジ-C₁~₁₀アルキルアミノ基、モノーもしくはジ-C₁~₁₀アルキルアミノスルホニル基、スルホ基、ホスホノ基、ビス（ヒドロキシカルボニル）メチル基、ビス（アルコキシカルボニル）メチル基、又は5-テトラゾリル基を表し、

R³は、水素原子、フッ素原子、塩素原子、臭素原子、水酸基、アミノ基、ニトロ基、C₁~₁₀アルキル基、C₁~₁₀アルコキシ基、カルボキシル基、又はC₁~₁₀アルコキシカルボニル基を表し、

X¹は、式

$$-\text{NH}-\text{CO}-\text{NH}-, -\text{N}(\text{R}^4)-, -\text{CO}-\text{N}(\text{R}^5)-, -\text{N}(\text{R}^5)-\text{CO}-, -\text{N}(\text{R}^5)-\text{SO}_2-, -\text{SO}_2-\text{N}(\text{R}^5)-,$$

〔式中、

R⁴は、水素原子、C₁~₁₀アルキル基、C₁~₁₀アルキルカルボニル基、C₁~₁₀アルキルスルホニル基を表し、

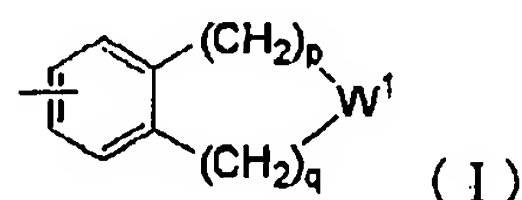
R⁵は、水素原子、C₁~₁₀アルキル基、アリール基を表す。）で示される構造を表し、

Y¹は、フェニル基、またはナフチル基、または1~2環性芳香族複素環基（これらの芳香環は、ハロゲン原子、水酸基、C₁~₁₀アルキル基、C₁~₁₀アルコキシ基、トリフルオロメチル基、アリール基、メチレンジオ

【化1】

キシ基、C₁~₁₀ヒドロキシアルキル基、カルボキシル基、C₁~₄アルコキシカルボニル基、C₁~₁₀アルキルスルフェニル基、C₁~₁₀アルキルスルフィニル基、C₁~₁₀アルキルスルホニル基、モノーもしくはジアルキルアミノ基、1-ピロリジノ基、1-ピペリジノ基、C₁~₁₀アミノアルキル基、モノーもしくはジアルキルアミノアルキル基、スルホ基、ホスホノ基などの置換基を1~3個有していてもよい。）、あるいは、下記式(I)

【化2】



〔式(I)中、

W¹は、結合、または式

-O-, -O-CO-, -N(R⁶)-

〔式中、

R⁶は、水素原子、C₁~₁₀アルキル基、C₁~₁₀アルキルカルボニル基、C₁~₁₀アルキルスルホニル基、またはアリール基を表す。）で示される構造を表し、p、qは、4 ≥ p + q ≥ 2（ただし、W¹が結合を示す場合は、4 ≥ p + q ≥ 3）を満たす0~3の整数を表す。）で示される基、あるいは下記式

-NH-CO-Z

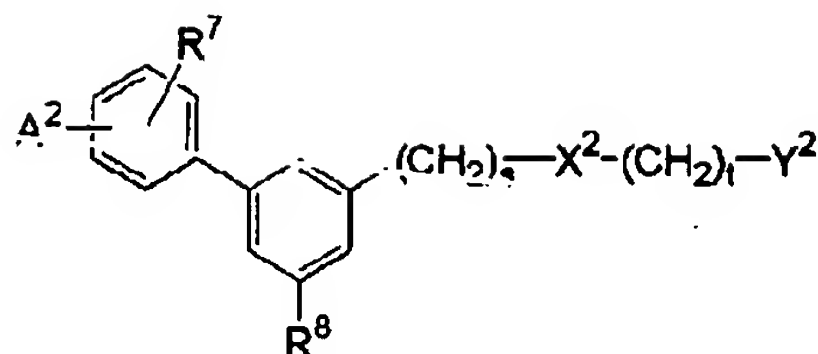
〔式中、ZはC₁~₁₀アルキル基またはアリール基（上記、Zのアルキル基またはアリール基は、C₁~₄アルキル基、水酸基、アミノ基、モノーもしくはジアルキルアミノ基、ハロゲン原子、C₁~₄アルコキシ基、カルボキシル基、C₁~₄アルコキシカルボニル基によって置換されていてもよい。）を表す。）で示される基を表し、

mは、1~3の整数を表し、

nは、0~3の整数（ただし、Y¹が式-NH-CO-Zで表される場合はnは0ではない。）を表す。〕で表されるビフェニルアミジン誘導体またはその薬学的に許容される塩。

【請求項2】 一般式(2)

【化3】



〔式(2)中、

A²はアミノ基を表し、

R⁷は、水素原子、フッ素原子、塩素原子、臭素原子、水酸基、アミノ基、ニトロ基、C₁~₄アルキル基、または、C₁~₄アルコキシ基を表し、

R⁸は、カルボキシル基、C₁~₄アルコキシカルボニル基、アリアルコキシカルボニル基、アラルコキシカルボニル基、カルバモイル基(カルバモイル基を構成する窒素原子は、モノーもしくはジ-C₁~₄アルキル基で置換されていてもよく、またはアミノ酸の窒素原子でもよい。)を表し、

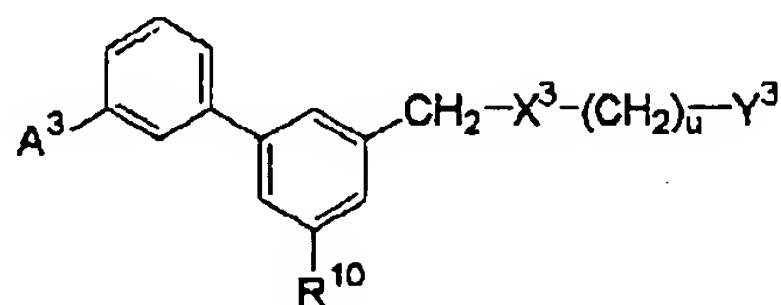
X²は、式

-NH-, -NH-CO-, -NH-SO₂-, -NH-CO-NH-

で示される構造を表し、

Y²は、フェニル基、またはナフチル基、または1~2環性芳香族複素環基(これらの芳香環は、ハロゲン原子、水酸基、C₁~₄アルキル基、C₁~₄アルコキシ基、トリフルオロメチル基、アリール基、メチレンジオキシ基、C₁~₄ヒドロキシアリル基、カルボキシル基、C₁~₄アルコキシカルボニル基、C₁~₄アルキルスルフェニル基、C₁~₄アルキルスルフィニル基、C₁~₄アルキルスルホニル基、モノーもしくはジ-アルキルアミノ基、1-ピロリジノ基、1-ピペリジノ基、C₁~₄アミノアルキル基、モノーもしくはジ-アルキルアミノアルキル基を1~3個有していてもよい。)、あるいは、下記式(II)

〔化4〕



〔式(3)中、

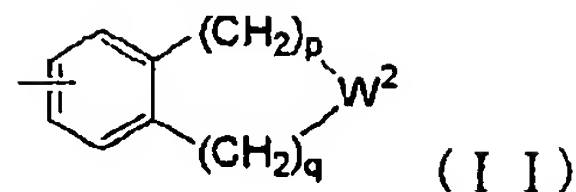
A³はアミノ基を表し、

R¹⁰は、カルボキシル基、C₁~₄アルコキシカルボニル基、アリアルコキシカルボニル基、アラルコキシカルボニル基、カルバモイル基(カルバモイル基を構成する窒素原子は、モノーもしくはジ-C₁~₄アルキル基で置換されていてもよく、またはアミノ酸の窒素原子でもよい。)を表し、

X³は、式

-NH-, -NH-CO-, -NH-SO₂-, -NH-CO-NH-

(2)



(II)

(式(II)中、

W²は、結合、または式

-O-, -N(R⁹)-

(式中、

R⁹は、水素原子、C₁~₁₀アルキル基、C₁~₁₀アルキルカルボニル基、C₁~₁₀アルキルスルホニル基、またはアリール基を表す。)で示される構造を表し、p、qは、4 ≥ p + q ≥ 2(ただし、W¹が結合を示す場合は、4 ≥ p + q ≥ 3)を満たす0~3の整数を表す。)で示される基、あるいは下記式

-NH-CO-Z

(式中、ZはC₁~₁₀アルキル基またはアリール基(上記、Zのアルキル基またはアリール基は、C₁~₄アルキル基、水酸基、アミノ基、モノーもしくはジアルキルアミノ基、ハロゲン原子、C₁~₄アルコキシ基、カルボキシル基、C₁~₄アルコキシカルボニル基によって置換されていてもよい。)を表す。)で示される基を表し、sは、1~2の整数を表し、

tは、0~2の整数(ただし、Y²が式: -NH-CO-Zで表される場合はtは0ではない。)を表す。〕で表されるビフェニルアミン誘導体またはその薬学的に許容される塩。

【請求項3】 一般式(3)

〔化5〕

(3)

で示される構造を表し、

Y³は、フェニル基、またはナフチル基、または1~2環性芳香族複素環基(これらの芳香環は、ハロゲン原子、水酸基、C₁~₄アルキル基、C₁~₄アルコキシ基、トリフルオロメチル基、メチレンジオキシ基、C₁~₄ヒドロキシアリル基、カルボキシル基、C₁~₄アルコキシカルボニル基、モノーもしくはジ-アルキルアミノ基、1-ピロリジノ基、1-ピペリジノ基、C₁~₄アミノアルキル基、モノーもしくはジ-アルキルアミノアルキル基を1~3個有していてもよい。)、あるいは、下記式

—NH—CO—Z

(式中、Zは $C_{1\sim 10}$ アルキル基またはアリール基(上記、Zのアルキル基またはアリール基は、 $C_{1\sim 4}$ アルキル基、水酸基、アミノ基、モノーもしくはジアルキルアミノ基、ハロゲン原子、 $C_{1\sim 4}$ アルコキシ基、カルボキシ基、 $C_{1\sim 4}$ アルコキシカルボニル基によって置換されていても良い。)を表す。)で示される基を表し、uは、0～1の整数(ただし、 Y^3 が式—NH—CO—Zで表される場合はuは0ではない。)を表す。)で表されるビフェニルアミジン誘導体またはその薬学的に許容される塩。

【請求項4】 上記式(3)の X^3 が、式—NH—CO—, —NH—SO₂—, —NH—CO—NH—

で表される請求項1～3いずれか1項記載のビフェニルアミジン誘導体またはその薬学的に許容される塩。

【請求項5】 上記式(3)の X^3 が、式—NH—

で表される請求項1～3いずれか1項記載のビフェニルアミジン誘導体またはその薬学的に許容される塩。

【請求項6】 生体内で、請求項1～5いずれか1項記載のビフェニルアミジン誘導体またはその薬学的に許容される塩を生成するそのプロドラッグ体。

【請求項7】 少なくとも請求項1～6いずれか1項記載の化合物またはその薬学的に許容される塩と薬学的に許容される担体とからなる血液凝固抑制剤。

【請求項8】 少なくとも請求項1～6いずれか1項記載の化合物またはその薬学的に許容される塩と薬学的に許容される担体とからなる血栓または塞栓の予防剤。

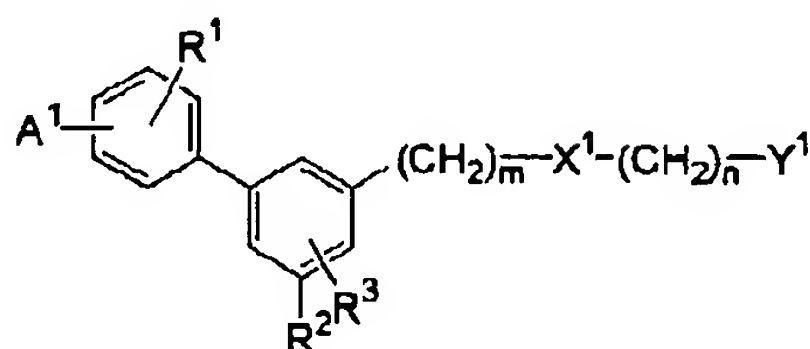
【請求項9】 少なくとも請求項1～6いずれか1項記載の化合物またはその薬学的に許容される塩と薬学的に許容される担体とからなる血栓または塞栓の治療剤。

【発明の詳細な説明】

【0001】

【発明の属する技術分野】本発明は式(1)で示される新規な選択的な活性化血液凝固第X因子(以下FXaと略す)抑制剤に関するものである。

【0002】



(1)

【0010】[式(1)中、 A^1 はアミノ基を表し、 R^1 は、水素原子、フッ素原子、塩素原子、臭素原子、水酸基、アミノ基、ニトロ基、 $C_{1\sim 10}$ アルキル基、または、 $C_{1\sim 10}$ アルコキシ基を表し、 R^2 は、フッ素原子、塩素原子、臭素原子、水酸基、アミノ基、 $C_{1\sim 10}$ アルコキシ基、カルボキシ基、 $C_{1\sim 10}$ アルコキシカル

【従来の技術】抗凝固療法は、心筋梗塞、脳血栓症、末梢動脈血栓症、深部静脈血栓症等の血栓塞栓性疾患に対して、内科的治療・予防法として重要な役割を担っている。

【0003】特に慢性の血栓症の予防に於いては、長期投与可能な安全かつ適切な経口抗凝固剤が必要である。しかし、現状では、抗凝固能のコントロールが難しいワルファリンカリウムが存在するだけであり、より使いやすい抗凝固剤が求められている。

【0004】抗トロンビン剤は、従来から抗凝固剤として開発が進められているが、例えば、ヒルジンに見られるような副作用として出血傾向をきたす危険性があることが知られていた。血液凝固カスケードでトロンビンの上流に位置するFXaの抑制は、機構的にトロンビンの抑制より効率的であり、かつFXa抑制剤においては、このような副作用が弱く、臨床的に望ましいことが明らかになってきた。

【0005】FXa阻害活性を示すビフェニルアミジン化合物が、第17回メディシナルケミストリーシンポジウム、第6回医薬化学部会年会要旨集、184-185、1997に記載されている。しかし、本発明化合物は、S1ポケットと相互作用するであろうビフェニルアミジン構造とアリール結合サイトと相互作用するであろう環状構造との結合にヘテロ原子を活用している点で構造上、明瞭に異なる新規な化合物である。

【0006】また、環状イミノ誘導体(特開平4-264068号公報)は、ビフェニルアミジン誘導体を開示しているが、本発明は、ベンジル位でヘテロ原子による結合をしている点で明瞭に異なる。

【0007】

【発明が解決しようとする課題】本発明の目的は、臨床応用可能なFXa抑制剤となり得る新規化合物を提供することである。

【0008】

【課題を解決するための手段】本発明者らは、上記目的を達成するため鋭意検討を重ねた結果、下記式(1)

【0009】

【化6】

ルボニル基、アリールオキシカルボニル基、アラルコキシカルボニル基、カルバモイル基(カルバモイル基を構成する窒素原子は、モノーもしくは、ジ- $C_{1\sim 10}$ アルキル基で置換されていても良く、またはアミノ酸の窒素原子でもよい。)、 $C_{1\sim 10}$ アルキルカルボニル基、 $C_{1\sim 10}$ アルキルスルフェニル基、 $C_{1\sim 10}$ アルキルスルフ

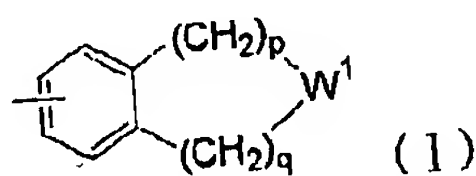
ニル基、 $C_1 \sim 10$ アルキルスルホニル基、モノもしくはジ- $C_1 \sim 10$ アルキルアミノ基、モノもしくはジ- $C_1 \sim 10$ アルキルアミノスルホニル基、スルホ基、ホスホ基、ビス(ヒドロキシカルボニル)メチル基、ビス(アルコキシカルボニル)メチル基、又は5-テトラゾリル基を表し、 R^3 は、水素原子、フッ素原子、塩素原子、臭素原子、水酸基、アミノ基、ニトロ基、 $C_1 \sim 10$ アルキル基、 $C_1 \sim 10$ アルコキシ基、カルボキシ基、又は $C_1 \sim 10$ アルコキシカルボニル基を表し、 X^1 は、式

$$-NH-CO-NH-, -N(R^4)-, -CO-N(R^5)-, -N(R^5)-CO-, -N(R^5)-SO_2-, -SO_2-N(R^5)-,$$

(式中、 R^4 は、水素原子、 $C_1 \sim 10$ アルキル基、 $C_1 \sim 10$ アルキルカルボニル基、 $C_1 \sim 10$ アルキルスルホニル基を表し、 R^5 は、水素原子、 $C_1 \sim 10$ アルキル基、アリール基を表す。)を表し、 Y^1 は、フェニル基、またはナフチル基、または1~2環性芳香族複素環基(これらの芳香環は、ハロゲン原子、水酸基、 $C_1 \sim 10$ アルキル基、 $C_1 \sim 10$ アルコキシ基、トリフルオロメチル基、アリール基、メチレンジオキシ基、 $C_1 \sim 10$ ヒドロキシアルキル基、カルボキシ基、 $C_1 \sim 4$ アルコキシカルボニル基、 $C_1 \sim 10$ アルキルスルフェニル基、 $C_1 \sim 10$ アルキルスルフィニル基、 $C_1 \sim 10$ アルキルスルホニル基、モノもしくはジ-アルキルアミノ基、1-ピロリジノ基、1-ピペリジノ基、 $C_1 \sim 10$ アミノアルキル基、モノもしくはジ-アルキルアミノアルキル基、スルホ基、ホスホ基などの置換基を1~3個有していてもよい。)を、あるいは、下記式(I)

【0011】

【化7】



【0012】(式(I)中、 W^1 は、結合、または式

$-O-$ 、 $-O-CO-$ 、 $-N(R^6)-$

(式中、 R^6 は、水素原子、 $C_1 \sim 10$ アルキル基、 $C_1 \sim 10$ アルキルカルボニル基、 $C_1 \sim 10$ アルキルスルホニル基、またはアリール基を表す。)で示される構造を表し、 p 、 q は、 $4 \geq p+q \geq 2$ (ただし、 W^1 が結合を示す場合は、 $4 \geq p+q \geq 3$)を満たす0~3の整数を表す。)で示される基、あるいは下記式

$-NH-CO-Z$

(式中、 Z は $C_1 \sim 10$ アルキル基またはアリール基(上記、 Z のアルキル基またはアリール基は、 $C_1 \sim 4$ アルキル基、水酸基、アミノ基、モノもしくはジアルキルアミノ基、ハロゲン原子、 $C_1 \sim 4$ アルコキシ基、カルボキシ基、 $C_1 \sim 4$ アルコキシカルボニル基によって置換されていてもよい。)を表す。)で示される基を表し、 m は、1~3の整数を表し、 n は、0~3の整数(ただ

し、 Y^1 が式： $-NH-CO-Z^1$ で表される場合は n は0ではない。)を表す。)で表されるビフェニルアミジン誘導体またはその薬学的に許容される塩を見だし、本発明を完成するに至ったものである。

【0013】以下、本発明について詳細に説明する。本明細書中の式(1)、式(2)または式(3)の化合物の置換基に対する上記の定義において、「 $C_1 \sim 4$ アルキル基」とは、炭素数1~4個を有する直鎖状、分枝状または環状の炭化水素基を意味し、例えば、メチル基、エチル基、プロピル基、イソプロピル基、ブチル基、イソブチル基、tert-ブチル基、シクロプロピル基等を表し、中でもメチル基、エチル基、プロピル基、イソプロピル基が好ましい。

【0014】「 $C_1 \sim 10$ アルキル基」とは、炭素数1~10個を有する直鎖状、分枝状または環状の炭化水素基を意味し、例えばメチル基、エチル基、プロピル基、イソプロピル基、ブチル基、イソブチル基、tert-ブチル基、ペンチル基、ネオペンチル基、イソペンチル基、1,2-ジメチルプロピル基、ヘキシル基、イソヘキシル基、1,1-ジメチルブチル基、2,2-ジメチルブチル基、1-エチルブチル基、2-エチルブチル基、ヘプチル基、イソヘプチル基、1-メチルヘキシル、2-メチルヘキシル、オクチル基、2-エチルヘキシル基、ノニル基、デシル基、又は1-メチルノニル基、シクロプロピル基、シクロブチル基、シクロペンチル基、シクロヘキシル基、シクロヘプチル基、シクロオクチル基、アダマンチル基等を表わし、中でもメチル基、エチル基、プロピル基、イソプロピル基、ブチル基、tert-ブチル基、シクロヘキシル基が好ましく、とくに置換基 Y^1 、 Y^2 、または Y^3 中に含まれる置換基である場合はメチル基、エチル基、イソプロピル基がとくに好ましい。

【0015】「アリール基」とは、具体的には、フェニル基、ナフチル基、チオフェニル基、ピリジル基などの芳香環基を意味し、好ましくは、フェニル基、ナフチル基である。

【0016】「アラルキル基」とは、具体的には、ベンジル基、フェネチル基、フェニルプロピル基、1-ナフチルメチル基、2-ナフチルメチル基等が挙げられ、好ましくはベンジル基である。

【0017】「 $C_1 \sim 4$ アルキルカルボニル基」としては、炭素数1~4個の直鎖又は分枝状または環状のアルキル側鎖を有するを持つカルボニル基を表わし、例えばホルミル基、アセチル基、プロピオニル基、ブチリル基、イソブチリル基、ピバロイル基等を意味し、好ましくは炭素数1~3個のアセチル基、プロピオニル基である。

【0018】「 $C_1 \sim 10$ アルキルカルボニル基」としては、炭素数1~10個を有する直鎖又は分枝状または環状の炭素鎖を持つカルボニル基を表し、例えばホルミル

基、アセチル基、プロピオニル基、ブチリル基、イソブチリル基、バレリル基、イソバレリル基、ピバロイル基、ヘキサノイル基、ヘプタノイル基、オクタノイル基、ノナノイル基、シクロペンチルカルボニル基、シクロヘキシルカルボニル基等を意味し、好ましくは炭素数1~8個のアセチル基、プロピオニル基、ブチリル基、ヘキサノイル基、オクタノイル基である。

【0019】「アリールカルボニル基」とは、ベンゾイル基、4-メトキシベンゾイル基、3-トリフルオロメチルベンゾイル基、又は複素環が結合したカルボニル基等を意味し、好ましくは、ベンゾイル基である。

【0020】「アリールオキシカルボニル基」とは、フェノキシカルボニル基、ナフチルオキシカルボニル基、4-メチルフェノキシカルボニル基、3-クロロフェノキシカルボニル基、4-メトキシフェノキシカルボニル基、又はインダン-5-イルオキシカルボニル基等を意味し、好ましくはフェノキシカルボニル基、インダン-5-イルオキシカルボニル基である。

【0021】「アラルコキシカルボニル基」とは、ベンジルオキシカルボニル基、4-メトキシベンジルオキシカルボニル基、3-トリフルオロメチルベンジルオキシカルボニル基、3-オキソヒドロイソベンゾフラニルオキシカルボニル基等を意味し、好ましくはベンジルオキシカルボニル基、3-オキソヒドロイソベンゾフラニルオキシカルボニル基である。

【0022】「 C_{1-4} アルコキシカルボニル基」とは、メトキシカルボニル基、エトキシカルボニル基、プロポキシカルボニル基、イソプロポキシカルボニル基、ブトキシカルボニル基、イソブトキシカルボニル基、sec-ブトキシカルボニル基、tert-ブトキシカルボニル基、アセトキシ基などの炭素数1~4のアルコキシカルボニル基で置換されたカルボニル基を意味し、好ましくは、メトキシカルボニル基、エトキシカルボニル基であり、とくに置換基 Y^1 、 Y^2 、または Y^3 中に含まれる置換基である場合は、メトキシカルボニル基、エトキシカルボニル基が好ましい。

【0023】「 C_{1-10} アルコキシカルボニル基」とは、メトキシカルボニル基、エトキシカルボニル基、プロポキシカルボニル基、イソプロポキシカルボニル基、ブトキシカルボニル基、イソブトキシカルボニル基、sec-ブトキシカルボニル基、tert-ブトキシカルボニル基、ペンチルオキシカルボニル基、イソペンチルオキシカルボニル基、ネオペンチルオキシカルボニル基、ヘキシルオキシカルボニル基、ヘプチルオキシカルボニル基、オクチルオキシカルボニル基、又は、アセトキシ基、ピバロイルオキシ基、又は、5-メチル-3-オキソ-2, 4-ジオキソレニル基などの炭素数1~10のアルコキシカルボニル基で置換されたメトキシカルボニル基、エトキシカルボニル基、プロポキシカルボニル基、イソプロ

ポキシカルボニル基、アセトキシメチルオキシカルボニル基、ピバロイルオキシメチルオキシカルボニル基、(5-メチル-3-オキソ-2, 4-ジオキソレニル)メチルオキシカルボニル基、エトキシカルボニルオキシエチルオキシカルボニル基であり、とくに置換基 Y^1 、 Y^2 、または Y^3 中に含まれる置換基である場合は、メトキシカルボニル基、エトキシカルボニル基が好ましい。

【0024】「 C_{1-4} アルコキシ基」とは、炭素数1~4個を有するアルコキシ基を意味し、具体的にはメトキシ基、エトキシ基、プロポキシ基、イソプロポキシ基、ブトキシ基、イソブトキシ基、sec-ブトキシ基、tert-ブトキシ基等であり、中でもメトキシ基、エトキシ基、イソプロピル基が好ましく、とくに置換基 Y^1 、 Y^2 、または Y^3 中に含まれる置換基である場合は、メトキシ基、エトキシ基が好ましい。

【0025】「 C_{1-10} アルコキシ基」とは、炭素数1~10個を有するアルコキシ基を意味し、具体的にはメトキシ基、エトキシ基、プロポキシ基、イソプロポキシ基、ブトキシ基、イソブトキシ基、sec-ブトキシ基、tert-ブトキシ基、ペンチルオキシ基、ネオペンチルオキシ基、tert-ペンチルオキシ基、2-メチルブトキシ基、ヘキシルオキシ基、イソヘキシルオキシ基、ヘプチルオキシ基、イソヘプチルオキシ基、オクチルオキシ基、イソオクチルオキシ基、シクロヘキシルオキシ基等であり、中でも炭素数1~6個のメトキシ基、エトキシ基、シクロヘキシル基が好ましく、とくに置換基 Y^1 、 Y^2 、または Y^3 中に含まれる置換基である場合は、メトキシ基、エトキシ基が好ましい。

【0026】「 C_{1-4} アルキルスルフェニル基」とは、炭素数1~4個を有するアルキルスルフェニル基を意味し、具体的にはメチルチオ基、エチルチオ基、ブチルチオ基、イソブチルチオ基等を表し、好ましくはメチルチオ基である。

【0027】「 C_{1-10} アルキルスルフェニル基」とは、炭素数1~10個を有するアルキルスルフェニル基を意味し、具体的にはメチルチオ基、エチルチオ基、ブチルチオ基、イソブチルチオ基、ペンチルチオ基、ヘキシルチオ基、ヘプチルチオ基、オクチルチオ基等を表し、好ましくはメチルチオ基である。

【0028】「 C_{1-4} アルキルスルフィニル基」とは、炭素数1~4個を有するアルキルスルフィニル基を意味し、具体的には、メチルスルフィニル基、エチルスルフィニル基、ブチルスルフィニル基等を表し、好ましくはメチルスルフィニル基である。

【0029】「 C_{1-10} アルキルスルフィニル基」とは、炭素数1~10個を有するアルキルスルフィニル基を意味し、具体的には、メチルスルフィニル基、エチルスルフィニル基、ブチルスルフィニル基、ヘキシルスルフィニル基、オクチルスルフィニル基等を表し、好ましくはメチルスルフィニル基である。

【0030】「 $C_{1\sim 4}$ アルキルスルホニル基」とは、炭素数1～4個を有するアルキルスルホニル基を意味し、具体的にはメチルスルホニル基、エチルスルホニル基、ブチルスルホニル基であり、好ましくはメチルスルホニル基である。

【0031】「 $C_{1\sim 10}$ アルキルスルホニル基」とは、炭素数1～10個を有するアルキルスルホニル基を意味し、具体的にはメチルスルホニル基、エチルスルホニル基、プロピルスルホニル基、イソプロピルスルホニル基、ブチルスルホニル基、イソブチルスルホニル基、ペンチルスルホニル基、イソペンチルスルホニル基、ネオペンチルスルホニル基、ヘキシルスルホニル基、ヘプチルスルホニル基、オクチルスルホニル基、ノニルスルホニル基、デシルスルホニル基、シクロヘキシルスルホニル基等を表し、中でも、炭素数1～8個のメチルスルホニル基、エチルスルホニル基、ブチルスルホニル基、ヘキシルスルホニル基、オクチルスルホニル基が特に好ましい。

【0032】「モノーもしくは、ジ-アルキルアミノ基」とは、メチルアミノ基、ジメチルアミノ基、エチルアミノ基、プロピルアミノ基、ジエチルアミノ基、イソプロピルアミノ基、ジイソプロピルアミノ基、ジブチルアミノ基、ブチルアミノ基、イソブチルアミノ基、*sec*-ブチルアミノ基、*tert*-ブチルアミノ基、ペンチルアミノ基、ヘキシルアミノ基、ヘプチルアミノ基、オクチルアミノ基、シクロペンチルアミノ基、シクロヘキシルアミノ基等を意味し、好ましくはメチルアミノ基、ジメチルアミノ基、エチルアミノ基、ジエチルアミノ基、プロピルアミノ基であり、とくに置換基 Y^1 、 Y^2 、または Y^3 中に含まれる置換基である場合は、ジメチルアミノ基、ジエチルアミノ基がとくに好ましい。

【0033】置換基 Y^1 、 Y^2 、または Y^3 中に含まれる「モノーもしくは、ジ-アルキルアミノアルキル基」とは、具体的にはメチルアミノメチル基、ジメチルアミノメチル基、ジエチルアミノメチル基、メチルアミノエチル基、ジメチルアミノエチル基、エチルアミノエチル基、ジエチルアミノエチル基、メチルアミノプロピル基、ジメチルアミノプロピル基、エチルアミノプロピル基、ジエチルアミノプロピル基、メチルアミノブチル基、ジメチルアミノブチル基等を意味し、好ましくは、ジメチルアミノメチル基、ジエチルアミノメチル基、ジエチルアミノエチル基である。

【0034】置換基 Y^1 、 Y^2 、または Y^3 中に含まれる「 $C_{1\sim 4}$ アミノアルキル基」とは、アミノ基で置換された炭素数1～4のアルキル基を表し、具体的にはアミノメチル基、1-アミノエチル基、2-アミノエチル基、1-アミノプロピル基、2-アミノプロピル基、3-アミノプロピル基などを意味し、好ましくは、アミノメチル基、1-アミノメチル基、2-アミノエチル基、1-アミノプロピル基である。

【0035】「モノーもしくは、ジ-アルキルアミノスルホニル基」とは、具体的にはメチルアミノスルホニル基、ジメチルアミノスルホニル基、エチルアミノスルホニル基、プロピルアミノスルホニル基、ジエチルアミノスルホニル基、イソプロピルアミノスルホニル基、ジイソプロピルアミノスルホニル基、ジブチルアミノスルホニル基、ブチルアミノスルホニル基、イソブチルアミノスルホニル基、*sec*-ブチルアミノスルホニル基、*tert*-ブチルアミノスルホニル基、ペンチルアミノスルホニル基、ヘキシルアミノスルホニル基、ヘプチルアミノスルホニル基、オクチルアミノスルホニル基等を意味し、好ましくはメチルアミノスルホニル基、ジメチルアミノスルホニル基、エチルアミノスルホニル基、ジエチルアミノスルホニル基、プロピルアミノスルホニル基であり、さらに好ましくはメチルアミノスルホニル基、ジメチルアミノスルホニル基である。

【0036】「ビス(アルコキシカルボニル)メチル基」とは、具体的にはビス(メトキシカルボニル)メチル基、ビス(エトキシカルボニル)メチル基等を表し、好ましくはビス(メトキシカルボニル)メチル基である。

【0037】「 $C_{1\sim 4}$ ヒドロキシアルキル基」とは、ヒドロキシ基で置換された炭素数1～4のアルキル基を表し、具体的にはヒドロキシメチル基、1-ヒドロキシエチル基、2-アミノエチル基、1-ヒドロキシプロピル基、2-ヒドロキシプロピル基、3-ヒドロキシプロピル基などを意味し、好ましくは、ヒドロキシメチル基、1-ヒドロキシエチル基、2-ヒドロキシエチル基、1-ヒドロキシプロピル基であり、とくに置換基 Y^1 、 Y^2 、または Y^3 中に含まれる置換基である場合は、ヒドロキシメチル基が好ましい。

【0038】置換基 Y^1 、 Y^2 、または Y^3 中に含まれる「1～2環性芳香族複素環」とは、ヘテロ原子として酸素原子、硫黄原子、および/または窒素原子を1～3個有する1～2環性芳香族複素環を意味し、具体的にはフラン環、チオフェン環、ピロール環、ピリジン環、ピラジン環、イミダゾール環、トリアゾール環、オキサゾール環、イソオキサゾール環、チアゾール環、チアジアゾール環、インドール環、ベンズイミダゾール環、ベンズトリアゾール環、キノリン環、イソキノリン環、ベンゾフラン環、ベンズチオフェン環であり、その好適な例としては、チオフェン環、チアゾール環、ピロール環、ピリジン環、インドール環、イミダゾール環、トリアゾール環、ベンズイミダゾール環、キノリン環が挙げられる。

【0039】本発明化合物(1)は、酸付加塩を形成する場合がある。また、置換基の種類によっては、塩基との塩を形成する場合もある。このような塩は医薬的に許容できる塩であれば特に限定されないが、具体的には塩酸塩、臭化水素酸塩、ヨウ化水素酸塩、リン酸塩、硝酸

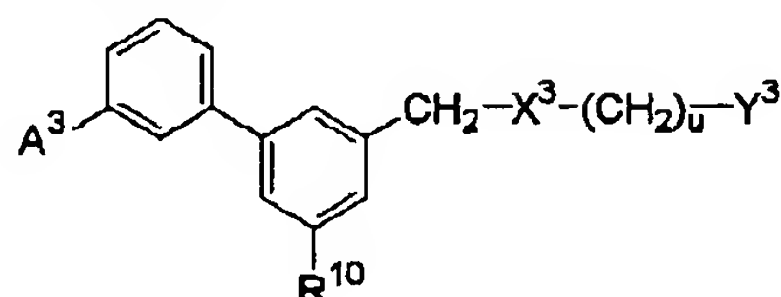
塩、硫酸塩等の鉱酸塩類；メタンスルホン酸塩、2-ヒドロキシエタンスルホン酸塩、p-トルエンスルホン酸塩等の有機スルホン酸塩；並びに酢酸塩、トリフルオロ酢酸塩、プロピオン酸塩、シュウ酸塩、マロン酸塩、コハク酸塩、グルタル酸塩、アジピン酸塩、酒石酸塩、マレイン酸塩、リンゴ酸塩、マンデル酸塩等の有機カルボン酸塩類が酸付加塩として含まれ、ナトリウム塩、カリウム塩、マグネシウム塩、カルシウム塩、アルミニウム

塩等の無機塩基との塩や、メチルアミン塩、エチルアミン塩、リジン塩、オルニチン塩等の有機塩基との塩が、塩基との塩として挙げられる。

【0040】本発明の化合物の好ましい範囲は、下記式(3)

【0041】

【化8】



(3)

【0042】〔式(3)中、A³はアミノ基を表し、R¹⁰は、カルボキシル基、C₁~₄アルコキシカルボニル基、アリールオキシカルボニル基、アラルコキシカルボニル基、カルバモイル基(カルバモイル基を構成する窒素原子は、モノーもしくはジ-C₁~₄アルキル基で置換されていても良く、またはアミノ酸の窒素原子でもよい。)を表し、X³は、式

-NH-, -NH-CO-, -NH-SO₂-, -NH-CO-NH-

で示される構造を表し、Y³は、フェニル基、またはナフチル基、または1~2環性芳香族複素環基(これらの芳香環は、ハロゲン原子、水酸基、C₁~₄アルキル基、C₁~₄アルコキシ基、トリフルオロメチル基、メチレンジオキシ基、C₁~₄ヒドロキシアルキル基、カルボキシル基、C₁~₄アルコキシカルボニル基、モノーもしくはジ-アルキルアミノ基、1-ピロリジノ基、1-ピペリジノ基、C₁~₄アミノアルキル基、モノーもしくはジ-アルキルアミノアルキル基を1~3個有していてもよい。)を、あるいは、下記式

-NH-CO-Z

(式中、ZはC₁~₁₀アルキル基またはアリール基(上記、Zのアルキル基またはアリール基は、C₁~₄アルキル基、水酸基、アミノ基、モノーもしくはジアルキルアミノ基、ハロゲン原子、C₁~₄アルコキシ基、カルボキシル基、C₁~₄アルコキシカルボニル基によって置換されていても良い。)を表す。)で示される基を表し、uは、0~1の整数(ただし、Yが式:-NH-CO-Zで表される場合はuは0ではない。)を表す。〕で表さ

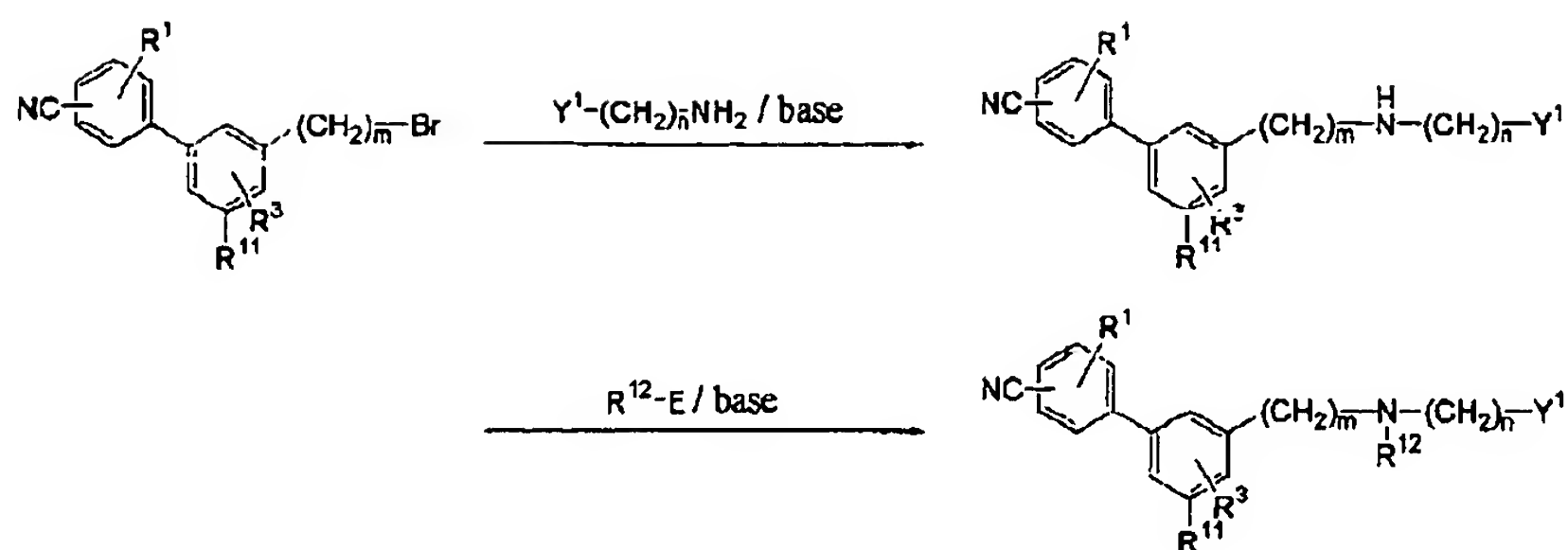
れるビフェニルアミジン誘導体またはその薬学的に許容される塩である。

【0043】以下に式(1)で表される本発明化合物の代表的な合成法を説明する。本発明においては、原料化合物または反応中間体が、反応に影響しうる水酸基、アミノ基、カルボキシル基などの置換基を有する場合、かかる官能基を適宜保護してエーテル化の反応を行い、しかる後に該保護基を脱離せしめることが望ましい。保護基としては、それぞれの置換基に対して通常用いられる保護基であって、保護、脱保護の工程で他の部分に悪影響を及ぼさない置換基であればとくに制限はなく、たとえば水酸基の保護基としては、トリアルキルシリル基、C₁~₄アルコキシメチル基、テトラヒドロピラニル基、アシル基、C₁~₄アルコキシカルボニル基などが挙げられ、アミノ基の保護基としては、C₁~₄アルコキシカルボニル基、ベンジルオキシカルボニル基、アシル基などが挙げられ、カルボキシル基の保護基としては、C₁~₄アルキル基などが挙げられる。脱保護反応はそれぞれの保護基に対して通常行われる方法に従って行うことができる。

【0044】式(1)で表される本発明化合物の前駆体であるニトリル体のうち、X¹として式:-N(R⁴)-で示される構造を持つ化合物は、たとえば、下記反応式(a-1)または(a-2)で示される反応によって合成できる。

【0045】

【化9】



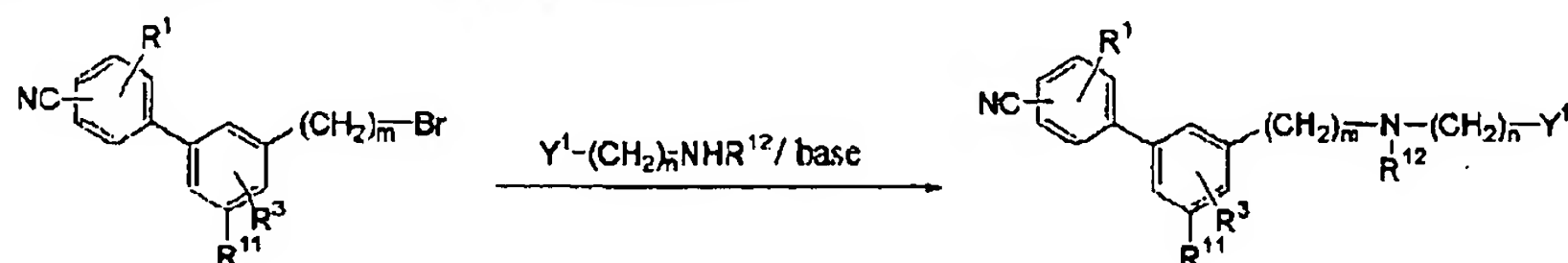
(a-1)

【0046】〔反応式中、 R^1 、 R^3 、 Y^1 、 m 、 n は式(1)における定義と等しく、 R^{11} は式(1)で定義される置換基 R^2 のうち、フッ素原子、塩素原子、臭素原子、水酸基(またはその保護体)、アミノ基(またはその保護体)、 $C_1\sim 10$ アルコキシ基、メトキシカルボニル基を意味し、 R^{12} は式(1)で定義される置換基 R^4

のうち水素原子、アリール基を除く置換基を意味し、 E は塩素、臭素、ヨウ素、アシロキシ基、スルホニルオキシ基などの脱離基を意味する。〕

【0047】

【化10】



(a-2)

【0048】〔反応式中、 R^1 、 R^3 、 Y^1 、 m 、 n は式(1)における定義と等しく、 R^{11} は式(1)で定義される置換基 R^2 のうち、フッ素原子、塩素原子、臭素原子、水酸基(またはその保護体)、アミノ基(またはその保護体)、 $C_1\sim 10$ アルコキシ基、メトキシカルボニル基を意味し、 R^{12} は式(1)で定義される置換基 R^4 のうちアリール基を意味し、 E は塩素、臭素、ヨウ素、アシロキシ基、スルホニルオキシ基などの脱離基を意味する。〕

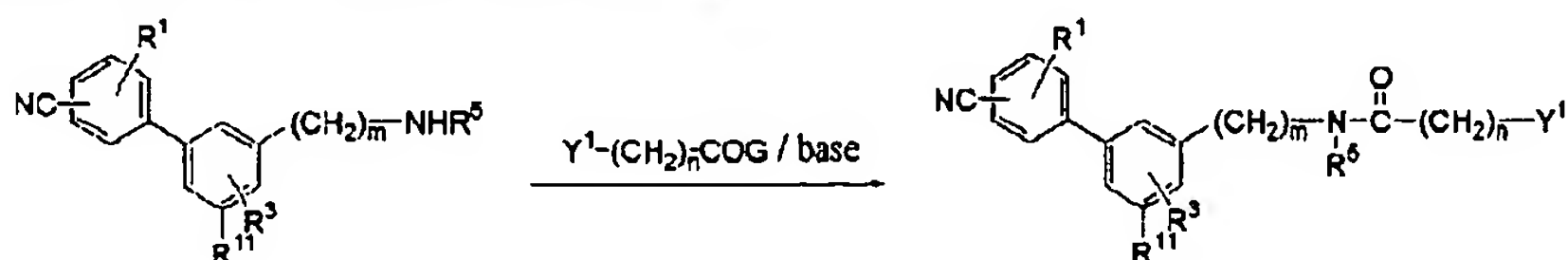
【0049】反応式(a-1)、(a-2)で示されるN-アルキル化反応は周知のアルキル化反応条件を用いて行うことができる。すなわち、原料のビフェニルアルキルブロミドに対し、塩基として作用する炭酸カリウムなどの無機塩や3級アミン類などのアミン類存在下、 $Y^1-(CH_2)_n-NH_2$ で表されるアミン類を反応させることにより、本発明化合物である2級アミン体が製造でき、2級アミン体に対して $R^{12}-E$ で表されるアルキル化剤を反応させるか、原料のビフェニルアルキルブロミドに対し、 $Y^1-(CH_2)_n-NHR^{12}$ で表されるアミン類を反応させることにより、本発明化合物である3級

アミン体を製造することができる。反応は通常、適当な溶媒中、アルキル化剤とアミンを任意の比で混合し、冷却ないし室温ないし加熱下、1～96時間攪拌して行われる。塩基としては炭酸カリウム、炭酸ナトリウムなどの無機塩やトリエチルアミン、ピリジンなどの有機3級アミン類を用い、溶媒としてはメタノール、エタノールなどのアルコール類、ベンゼン、トルエンなどの炭化水素類、あるいはTHF、ジオキサン、アセトニトリル、DMF、DMSOなどの反応に影響しない溶媒類、もしくはそれらの混合溶媒が用い、アルキル化剤とアミン体の比を1:10～10:1にして行われる。好ましくはアルキル化剤とアミン体の比を1:5～1:1にして、室温ないし加熱下、2～24時間行われる。

【0050】また、式(1)で表される本発明化合物の前駆体であるニトリル体のうち、 X^1 としてアミド結合を有する化合物は、たとえば、下記反応式(b-1)または(b-2)で示される反応によって合成できる。

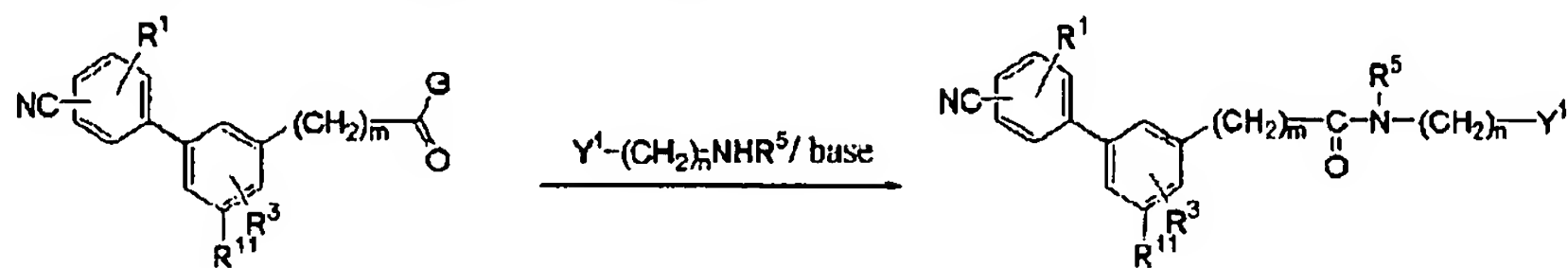
【0051】

【化11】



(b-1)

【0052】[反応式中、 R^1 、 R^3 、 R^5 、 Y^1 、 m 、 n は式(1)における定義と等しく、 R^{11} は式(1)で定義される置換基 R^2 のうち、フッ素原子、塩素原子、臭素原子、水酸基(またはその保護体)、アミノ基(またはその保護体)、 $C_1\sim 10$ アルコキシ基、メトキシカル



(b-2)

【0054】[反応式中、 R^1 、 R^3 、 R^5 、 Y^1 、 m 、 n は式(1)における定義と等しく、 R^{11} は式(1)で定義される置換基 R^2 のうち、フッ素原子、塩素原子、臭素原子、水酸基(またはその保護体)、アミノ基(またはその保護体)、 $C_1\sim 10$ アルコキシ基、メトキシカルボニル基を意味し、 G はハロゲン、アシロキシ基、 p -ニトロフェノキシ基、水酸基などの基を意味する。]

【0055】上記反応式(b-1)または(b-2)の反応は周知のアミド化反応の条件を用いることにより行うことができる。通常、塩基の存在下、カルボン酸の活性誘導体とアミン化合物を適当な溶媒中混合し、アシル化を行うことによりアミド体を得ることができる。用いるカルボン酸の活性誘導体としては、酸ハライド、混合酸無水物、 p -ニトロフェノールなどの活性エステル類などが用いられ、冷却ないし室温下において30分~24時間行われる。好ましくは塩基としてトリエチルアミンなどの3級アミン類を用い、ジクロロメタンなどのハロゲン化炭化水素類、THFやジエチルエーテルなどの脂肪族エーテル類、アセトニトリル、DMFなどの溶

媒またはそれらの混合溶媒中、0~20℃にて1~18時間行われる。

【0053】

【化12】

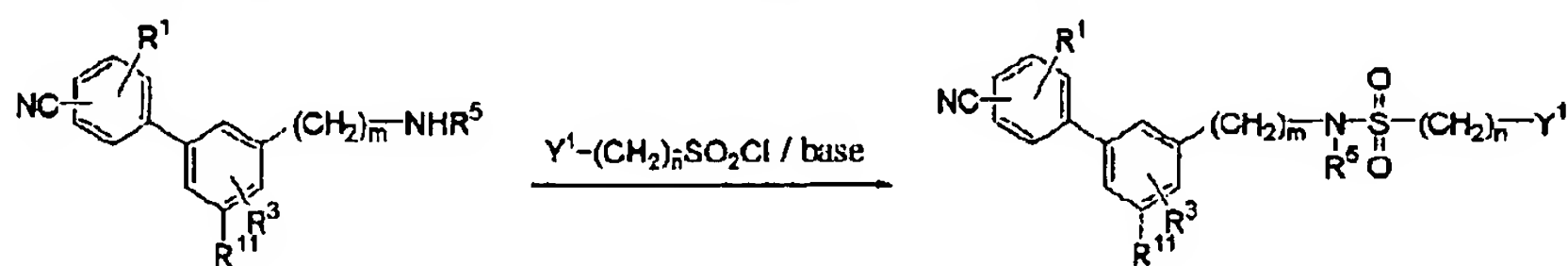
媒またはそれらの混合溶媒中、0~20℃にて1~18時間行われる。

【0056】また、このようなアミド体はカルボジイミド類などの縮合剤存在下、アミン類とカルボン酸の縮合反応によっても得ることができる。この場合、溶媒としてはDMFやクロロホルムなどのハロゲン化炭化水素類が適しており、縮合剤としては、 N 、 N -ジシクロヘキシルカルボジイミドや1-エチル-3-(N 、 N -ジメチルアミノ)プロピル)カルボジイミドやカルボニルジイミダゾール、ジフェニルホスホリルアジドやジエチルホスホリルシアニドが好適である。反応は通常、冷却ないし室温下で2~48時間行われる。

【0057】また、式(1)で表される本発明化合物の前駆体であるニトリル体のうち、 X^1 としてスルホンアミド構造を有する化合物は、たとえば、下記反応式(c-1)または(c-2)で示される反応によって合成できる。

【0058】

【化13】



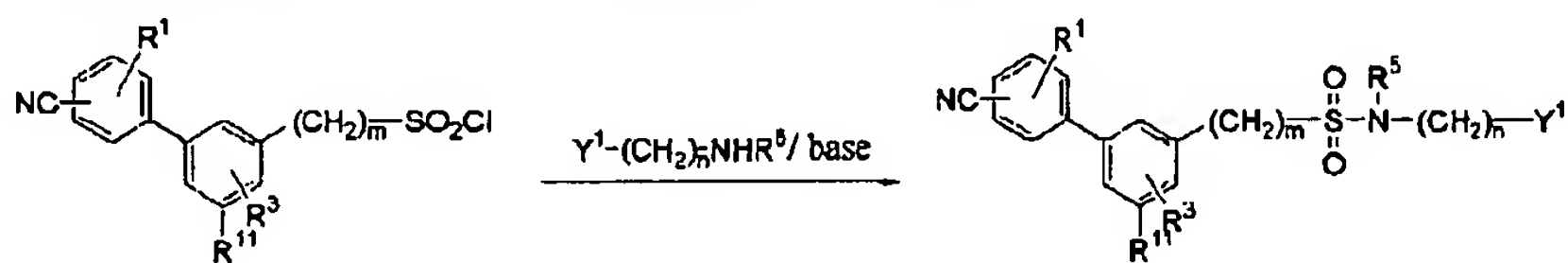
(c-1)

【0059】[反応式中、 R^1 、 R^3 、 R^5 、 Y^1 、 m 、 n は式(1)における定義と等しく、 R^{11} は式(1)で定義される置換基 R^2 のうち、フッ素原子、塩素原子、臭素原子、水酸基(またはその保護体)、アミノ基(また

はその保護体)、 $C_1\sim 10$ アルコキシ基、メトキシカルボニル基を意味する。]

【0060】

【化14】



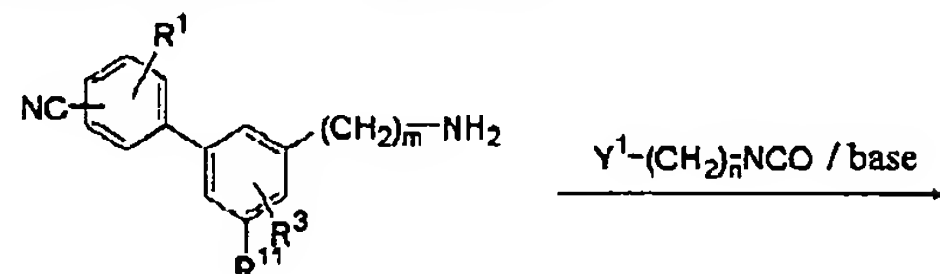
(c-2)

【0061】[反応式中、 R^1 、 R^3 、 R^5 、 Y^1 、 m 、 n は式(1)における定義と等しく、 R^{11} は式(1)で定義される置換基 R^2 のうち、フッ素原子、塩素原子、臭素原子、水酸基(またはその保護体)、アミノ基(また

はその保護体)、 $C_1\sim 10$ アルコキシ基、メトキシカルボニル基を意味する。]

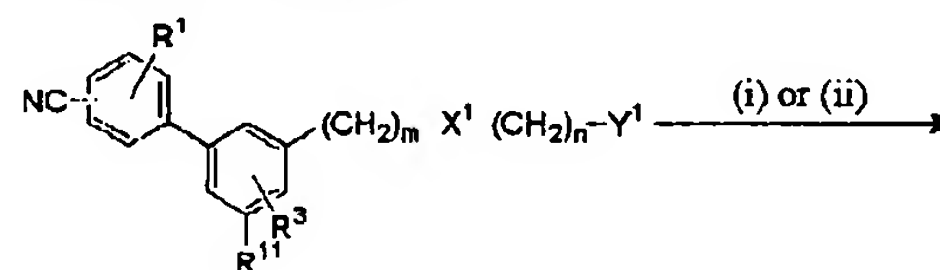
【0062】反応式(c-1)または(c-2)で表される反応は塩基の存在下、適当な溶媒中、アミンと

スルホン酸の活性誘導体を反応させて行い、目的のスルホンアミド体を取得できる。スルホン酸の活性誘導体としてはスルホニルハライドが好適であり、塩基としてトリエチルアミンなどの3級アミン類を用い、ジクロロメタンなどのハロゲン化炭化水素類、THFやジエチルエーテルなどの脂肪族エーテル類、アセトニトリル、DMFなどの溶媒またはそれらの混合溶媒中、0～20℃に



【0065】[反応式中、 R^1 、 R^3 、 Y^1 、 m 、 n は式(1)における定義と等しく、 R^{11} は式(1)で定義される置換基 R^2 のうち、フッ素原子、塩素原子、臭素原子、水酸基（またはその保護体）、アミノ基（またはその保護体）、 $C_1\sim 10$ アルコキシ基、メトキシカルボニル基を意味する。]

【0066】すなわち、 X^1 としてウレア構造をもつ化合物は、原料のアミンとイソシアナート誘導体とを適当な溶媒中冷却ないし加熱下反応させることにより製造できる。この反応で用いる溶媒はDMF、THF、ジオキ



【0069】[反応式中、 R^1 、 R^3 、 X^1 、 Y^1 、 m 、 n は式(1)における定義と等しく、 R^{11} は式(1)で定義される置換基 R^2 のうち、フッ素原子、塩素原子、臭素原子、水酸基（またはその保護体）、アミノ基（またはその保護体）、 $C_1\sim 10$ アルコキシ基、メトキシカルボニル基を意味し、 R^{13} は水素原子、水酸基、アミノ基、 $C_1\sim 10$ アルキル基、アリール基、アラルキル基を意味する。]に示すようなアミジノ化反応を施すことにより、本発明化合物であるベンズアミジン誘導体へと変換できる。このアミジノ化反応は以下の(i)または(ii)に示すような反応条件により行われる。

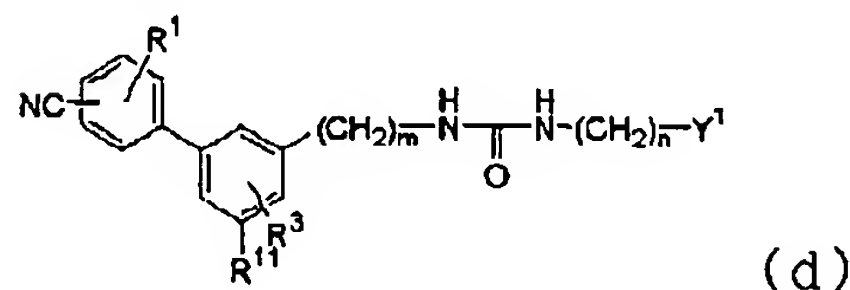
【0070】(i) ハロゲン化水素のアルコール溶液を用いたイミダート化を経るアミジノ化反応：ニトリル体とアルコール類からイミダートを得る反応は、たとえば、アルコキシメチルフェニルベンゾニトリル体を塩化水素、臭化水素などのハロゲン化水素を含有する炭素数1～4のアルコール類に溶解して攪拌することにより進行する。反応は通常、-20～30℃にて12～96時間行われる。好ましくは塩化水素のメタノールもしくはエタノール溶液中、-10～+30℃で24～72時間行われる。イミダートとアンモニアの反応は、イミダートをアンモニアを含むメタノール、エタノールなどの炭素数1～4のアルコール類、またはジエチルエーテルな

て1～24時間行われる。

【0063】また、式(1)で表される本発明化合物の前駆体であるニトリル体のうち、 X^1 としてウレア構造を有する化合物は、たとえば、下記反応式(d)で示される反応によって合成できる。

【0064】

【化15】

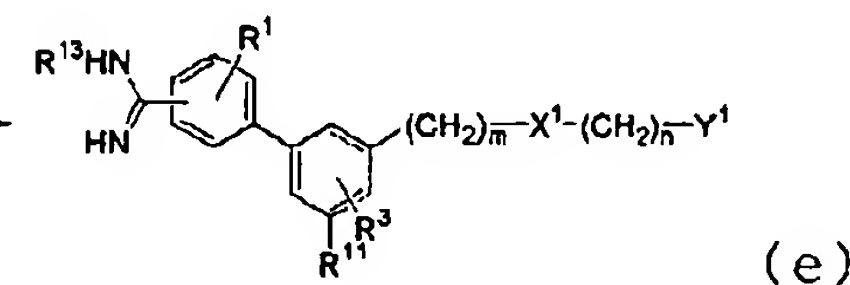


サン、ジクロロエタン、クロロホルム、アセトニトリル、DMSO、ベンゼン、トルエンなどである。

【0067】以上、上記反応式(a-1)、(a-2)、(b-1)、(b-2)、(c-1)、(c-2)、(d)で示される反応によって製造される、本発明化合物の前駆体であるニトリル体は、下記反応式(e)

【0068】

【化16】



どの脂肪族エーテル類、またはジクロロメタン、クロロホルムなどのハロゲン化炭化水素類、もしくはそれらの混合溶媒中で攪拌することにより進行し、本発明化合物であるベンズアミジン誘導体(1)が生成する。反応は通常、-10～+50℃の温度で1～48時間行われる。好ましくはメタノールまたはエタノール中、0～30℃にて2～12時間行われる。

【0071】(ii) ハロゲン化水素を直接吹き込みながら調整したイミダートを経るアミジノ化反応：ニトリル体とアルコールの反応は、たとえば、ニトリル体を、ジエチルエーテルなどの脂肪族エーテル類、もしくはクロロホルムなどのハロゲン化炭化水素類、もしくはベンゼンなどの非プロトン性溶媒に溶解し、当量もしくは過剰の炭素数1～4のアルコール類を加えて攪拌しながら、-30～0℃にて塩化水素や臭化水素のハロゲン化水素を30分～6時間吹き込み、その後吹き込みを止め、0～50℃にて3～96時間攪拌することにより進行する。好ましくは、当量もしくは過剰のメタノールもしくはエタノールを含むハロゲン化炭化水素類中攪拌しながら、-10～0℃にて、1～3時間塩化水素を吹き込み、その後吹き込みを止め、10～40℃にて8～24時間攪拌する。このようにして得られたイミダートは、アンモニアを含むメタノール、エタノールなどの炭

素数1～4のアルコール溶媒、またはジエチルエーテルなどの脂肪族エーテル溶媒、またはクロロホルムなどのハロゲン化炭化水素溶媒、もしくはそれらの混合溶媒中で攪拌することにより、本発明化合物であるベンズアミジン誘導体(1)に変換できる。反応は通常、 $-20 \sim +50^{\circ}\text{C}$ の温度で1～48時間行われる。好ましくは飽和アンモニアエタノール中、 $0 \sim 30^{\circ}\text{C}$ にて2～12時間行われる。

【0072】また、式(1)で示される化合物のうち、 R^2 としてカルボキシ基を有する化合物については、上記反応式(e)によって製造されるベンズアミジン化合物のうち、 R^3 としてメトキシカルボニル基をもつ化合物のエステル加水分解によって製造される。この加水分解反応は、必要に応じ、塩基性条件下、酸性条件下、あるいは中性条件下に行うことができる。塩基性条件下の反応では、用いる塩基としては水酸化ナトリウム、水酸化カリウム、水酸化リチウム、水酸化バリウム等が挙げられ、酸性条件下では塩酸、硫酸、三塩化ホウ素などのルイス酸、トリフルオロ酢酸、p-トルエンスルホン酸等が挙げられ、中性条件下ではヨウ化リチウム、臭化リチウムなどのハロゲンイオン、チオールまたはセレノールのアルカリ金属塩、ヨードトリメチルシラン、またはエステラーゼなどの酵素が挙げられる。反応に用いる溶媒としては、水、アルコール、アセトン、ジオキサン、THF、DMF、DMSOなどの極性溶媒、もしくはそれらの混合溶媒が用いられる。反応は通常、室温または加温下で2～96時間行う。反応温度や反応時間などの好適な条件は用いる反応条件によって異なり、常法により適宜選択して行う。

【0073】このようにして得られた、置換基 R^2 としてカルボキシ基を有する化合物については、以下の(iii)、(iv)、(v)に示す方法によって、カルボキシ基を他のエステル体に変換することができる。

【0074】(iii)カルボキシ基のアルコキシカルボニル基への変換：式(4)で表わされる化合物のうち、置換基 R^2 としてカルボキシ基を有する化合物と、当量もしくは過剰のアルキル化剤(たとえば、アセトキシ塩化メチル、ピバロイロキシ塩化メチルなどのアシロキシ塩化メチル類、または塩化アリル類、または塩化ベンジル類)を、ジクロロメタンなどのハロゲン化炭化水素類またはTHFなどの脂肪族エーテル類またはDMFなどの非プロトン性極性溶媒もしくはそれらの混合溶媒中、トリエチルアミンやジイソプロピルエチルアミン等の3級アミン類存在下、 $-10 \sim +80^{\circ}\text{C}$ において、1～48時間反応させることにより、カルボキシ基をアルコキシカルボニル基へ変換することができる。好ましくは、当量～小過剰のアルキル化剤を用い、ジイソプロピルエチルアミン存在下、 $20 \sim 60^{\circ}\text{C}$ にて2～24時間行われる。

【0075】(iv)カルボキシ基のアルコキシカルボニル基への変換：式(4)で表わされる化合物のうち、置換基 R^2 としてカルボキシ基を有する化合物と、当量もしくは過剰のベンジルアルコールなどのアルコール類を、ジクロロメタンなどのハロゲン化炭化水素類を溶媒として、塩化水素、硫酸、スルホン酸などの酸触媒存在下反応させると、カルボキシ基をアルコキシカルボニル基へ変換することができる。反応は通常、室温または加熱下で1～72時間行われる。好ましくは、当量～小過剰のアルコール類を用い、ジイソプロピルエチルアミン存在下、 $20 \sim 60^{\circ}\text{C}$ にて2～24時間行われる。

【0076】(v)カルボキシ基のアリールオキシカルボニル基への変換：式(4)で表わされる化合物のうち、置換基 R^2 としてカルボキシ基を有する化合物と、当量もしくは過剰のフェノールなどの水酸基を有する芳香族化合物を、ジエチルエーテルなどの脂肪族エーテル類を溶媒として、ジシクロヘキシルカルボジイミドなどの縮合剤存在下反応させると、カルボキシ基をアリールオキシカルボニル基へ変換することができる。反応は通常、 $0 \sim 50^{\circ}\text{C}$ にて1～48時間行われる。好ましくは、室温にて3～24時間行われる。

【0077】また、 R^2 としてカルボキシ基を有する化合物は、周知の手法、たとえばカルボキシ基をオキサリクロリドなどによって酸ハライドとし、アンモニア水を反応させることで、カルバモイル基に変換することもできる。同様に酸ハライドとN-メチル-N-メトキシアミンと反応させることにより、N-メチル-N-メトキシカルバモイル基に変換でき、これはさらに種々のアルキルマグネシウム反応剤と反応して、アルキルカルボニル基へと変換できる。

【0078】なお、式(1)で示される化合物はその他公知のエーテル化、アミノ化、加水分解、アルキルイミドイル化、アミド化、エステル化など、当業者が通常採用しうる工程を任意に組み合わせることにより製造することができる。

【0079】以上のようにして製造されるアルコキシメチルフェニルベンズアミジン誘導体Iは周知の方法、たとえば、抽出、沈殿、分画クロマトグラフィー、分別結晶化、再結晶等により、単離、精製することができる。また、本発明化合物の薬学的に許容される塩は、通常の造塩反応を施すことにより製造できる。

【0080】本発明のビフェニルアミジン誘導体またはその薬学的に許容される塩は、FXa活性を抑制する効果があり、FXa抑制剤として、心筋梗塞、脳血栓症、抹消動脈血栓症、深部静脈血栓症等の血栓塞栓性疾患に対して臨床応用可能な予防剤および/または治療剤として使用することが可能である。

【0081】また、本発明のビフェニルアミジン誘導体は、製薬学的に許容される担体とからなる医薬組成物と

し、該医薬組成物を種々の剤型に成型して経口あるいは非経口によって投与することができる。非経口投与としては、例えば、静脈、皮下、筋肉、経皮、直腸、経鼻、点眼内への投与が挙げられる。

【0082】該医薬組成物の剤型としては、以下のようなものが挙げられる。例えば、経口投与剤の場合は、錠剤、丸剤、顆粒剤、散剤、液剤、懸濁剤、シロップ剤、カプセル剤等の剤型が挙げられる。

【0083】ここで、錠剤の成型方法としては、賦形剤、結合剤、崩壊剤等の製薬学的に許容される担体を用いて通常の方法により成型することができる。丸剤、顆粒剤、散剤も錠剤の場合と同様に賦形剤等を用いて通常の方法により成型することができる。液剤、懸濁剤、シロップ剤の成型方法は、グリセリンエステル類、アルコール類、水、植物油等を用いて通常の方法により成型することができる。カプセル剤の成型方法は、顆粒剤、散剤、あるいは液剤等を、ゼラチン等のカプセルに充填することによって成型することができる。

【0084】非経口投与剤のうち、静脈、皮下、筋肉内投与の場合には、注射剤として投与することができる。注射剤としては、ビフェニルアミジン誘導体を、例えば生理食塩水など水溶性液剤に溶解する場合、あるいは、例えばプロピレングリコール、ポリエチレングリコール、植物油等の有機エステルからなる非水溶性液剤に溶解する場合等が挙げられる。

【0085】経皮投与の場合には、例えば軟膏剤、クリーム剤などの剤型として用いることができる。軟膏剤は、ビフェニルアミジン誘導体を油脂類、ワセリン等と混合して用いて、クリーム剤はビフェニルアミジン誘導体を乳化剤と混合して成型することができる。

【0086】直腸投与の場合には、ゼラチンソフトカプセルなどを用いて坐剤とすることができる。

【0087】経鼻投与の場合には、液状または粉末状の組成物からなる製剤として用いることができる。液状剤の基剤としては、水、食塩水、リン酸緩衝液、酢酸緩衝液等が用いられ、更に、界面活性剤、酸化防止剤、安定剤、保存剤、粘性付与剤を含んでもよい。粉末状剤の基剤としては、例えば、水易溶性のポリアクリル酸塩類、セルロース低級アルキルエーテル類、ポリエチレングリコールポリビニルピロリドン、アミロース、プルラン等の水吸収性のもの、あるいは、例えば、セルロース類、澱粉類、タンパク類、ガム類、架橋ビニル重合体類等の水難溶性ものが挙げられ、水吸収性のものが好ましい。また、これらを混合して用いてもよい。さらに粉末状剤には、酸化防止剤、着色剤、保存剤、防腐剤、矯腐剤等を添加してもよい。かかる液状剤、粉末状剤は、例えばスプレー器具等を用いて投与することができる。

【0088】点眼内投与の場合は、水性あるいは非水性の点眼剤として使用することができる。水性点眼剤としては、溶剤に滅菌精製水、生理食塩水等を用いることが

できる。溶剤として滅菌精製水のみを用いた場合、界面活性剤、高分子増粘剤等の懸濁剤を加えて水性懸濁点眼液として用いることができ、また、非イオン性界面活性剤等の可溶化剤を加えて可溶化点眼液として用いることもできる。非水性点眼剤としては、溶剤に注射用非水性溶剤を用いることができ、非水性懸濁点眼液として用いることができる。

【0089】点眼剤以外の方法で眼に投与する場合としては、眼軟膏剤、塗布液剤、散布剤、インサート剤等の剤型とすることができる。

【0090】また、鼻、口等から吸入する場合においては、ビフェニルアミジン誘導体と一般的に用いられる製薬賦形剤との溶液または懸濁液として、例えば、吸入用エアゾルスプレー等を用いて吸入される。また、乾燥粉末状としたビフェニルアミジン誘導体を、肺と直接接触させる吸入器等を用いて投与することができる。

【0091】これら種々の製剤には、必要に応じて、等張化剤、保存剤、防腐剤、湿潤剤、緩衝剤、乳化剤、分散剤、安定剤等の製薬学的に許容される担体を添加することができる。

【0092】また、これら種々の製剤には、必要に応じて、殺菌剤の配合、バクテリア保留フィルターを用いた濾過、加熱、照射等の処置を行い無菌化することができる。あるいは、無菌の固形製剤を製造し、使用直前に適当な無菌溶液に溶解あるいは懸濁して使用することもできる。

【0093】本発明のビフェニルアミジン誘導体の投与量は、疾患の種類、投与経路、患者の症状、年齢、性別、体重等により異なるが、一般的に、経口投与では1～500mg/日/人程度であり、好ましくは10～300mg/日/人である。静脈、皮下、筋肉、経皮、直腸、経鼻、点眼、吸入などの非経口的投与では、0.1～100mg/日/人程度であり、好ましくは0.3～30mg/日/人である。

【0094】また、本発明のビフェニルアミジン誘導体を予防剤として用いる場合には、各症状に応じて、予め公知の方法に従い投与することができる。

【0095】

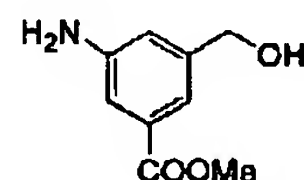
【実施例】本発明を以下に製造例、実施例及び試験例によって具体的に説明する。しかし、本発明の範囲がこれらの実施例によっていかなる意味においても制限されるものではない。

【0096】〔製造例1〕

3-アミノ-5-ヒドロキシメチル安息香酸メチルエステル

【0097】

【化17】



【0098】3-ニトロ-5-メトキシカルボニル安息香酸85gを窒素気流下でTHF200mlに溶かし、氷冷撹拌しながらボランジメチルスルフィド錯体43.4mlを加えた。18時間撹拌した後、200mlの水を加え炭酸カリウム96gを加えた。酢酸エチルで抽出し、有機層を食塩水で洗浄した。硫酸マグネシウムで乾燥した後、得られた固体を酢酸エチル800mlに溶かし、10%Pd/C750mgを加え、水素気流下で撹拌した。反応終了後、濾過を行った後に濾液を濃縮し、表題の化合物64gを得た。

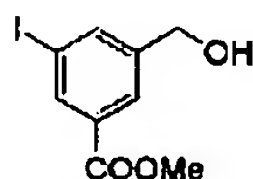
$^1\text{H-NMR}$ (270MHz, CDCl_3): δ 2.30 (s, 1H), 3.89 (s, 3H), 4.64 (s, 1H), 6.89 (s, 1H), 7.26 (s, 1H), 7.39 (s, 1H).

【0099】[製造例2]

5-ヒドロキシメチル-3-ヨード安息香酸メチルエステル

【0100】

【化18】



【0101】製造例1で得た化合物34.3gをTHF200mlに溶かし、氷冷撹拌しながらヨウ化水素酸75gを加えた。撹拌しながら亜硝酸ナトリウム13.73gの100ml水溶液を加えた。0℃で40分間撹拌した後、ヨウ化カリウム34.6gの150ml水溶液を加えた。40℃で2時間撹拌した後、300mlの水を加えて濃縮した。酢酸エチルで抽出し、有機層を食塩水で洗浄した。硫酸ナトリウムで乾燥した後、シリカゲルカラムクロマトグラフィーで精製し、表題の化合物23.1g (42%)を得た。

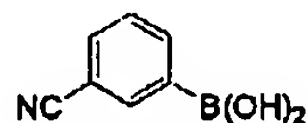
$^1\text{H-NMR}$ (270MHz, CDCl_3): δ 1.81 (t, 1H, $J=5.6\text{ Hz}$), 3.92 (s, 3H), 4.72 (d, 1H, $J=5.6\text{ Hz}$), 7.93 (s, 1H), 7.98 (s, 1H), 8.29 (s, 1H).

【0102】[製造例3]

ジヒドロキシー(3-シアノフェニル)ボラン

【0103】

【化19】



【0104】3-ブロモベンゾニトリル20gを乾燥THF100mlに溶かし、窒素雰囲気下で、トリイソプロポキシボラン37.6mlを加えた。この溶液を-78℃に冷却し、撹拌しながら、1.6Mn-ブチルリチウムヘキサン溶液98.3mlを約30分間で滴下した。室温で30分撹拌した後、0℃に冷却し、4M硫酸を220ml加えた。この溶液を一晚、加熱環流したの

ちに再び0℃に冷却し、5M水酸化ナトリウム水溶液340mlを加え、ジエチルエーテル200mlで抽出した。水層を分け、6M塩酸をpH2になるまで加えた。酢酸エチル300mlで2回抽出し、硫酸マグネシウムで乾燥した後、溶媒を留去した。得られた粗生成物をDMF-水から再結晶し、表題の化合物11.6g (72%)を針状の淡黄色結晶として得た。

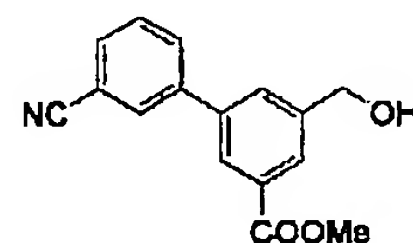
$^1\text{H-NMR}$ (270MHz, $\text{DMSO}-d_6$): δ 7.6~8.3 (m, 4H), 8.5 (brs, 2H).

【0105】[製造例4]

3-(3-シアノフェニル)-5-(ヒドロキシメチル)安息香酸メチルエステル

【0106】

【化20】



【0107】製造例2で得た化合物3.08gを、窒素気流下、乾燥DMF50mlに溶解し、この溶液に製造例3で得た化合物2.32g、炭酸カリウム2.18gおよびテトラキス(トリフェニルフォスフィン)パラジウム456mgを加え、90℃で一晩、加熱撹拌した。水を加えて反応を停止し、酢酸エチルで抽出し、硫酸マグネシウムで乾燥した後、溶媒を留去した。シリカゲルカラムクロマトグラフィーで精製し、表題の化合物を2.05g (73%)、無色結晶として得た。

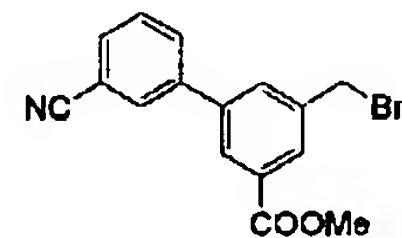
$^1\text{H-NMR}$ (270MHz, CDCl_3): δ 2.1 (brs, 1H), 3.96 (s, 3H), 4.84 (d, 2H, $J=3.7\text{ Hz}$), 7.5~8.2 (m, 7H).

【0108】[製造例5]

3-(3-シアノフェニル)-5-(ブロモメチル)安息香酸メチルエステル

【0109】

【化21】



【0110】製造例4で得られた化合物1.0gにジエチルエーテル20mlを加えて懸濁液とした後に三臭化リン0.5mlをゆっくり滴下した。反応液は室温下19時間撹拌した後に、抽出を行った。有機層は飽和食塩水で洗浄し、硫酸ナトリウムで乾燥した後、減圧下溶媒を留去すると、表題の化合物が淡黄色の固体として得られた(1.2g, 98%)。

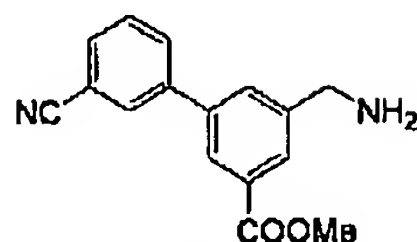
$^1\text{H-NMR}$ (270MHz, CDCl_3): δ 3.97 (s, 3H), 4.58 (s, 2H), 7.5~7.9 (m, 5H), 8.1~8.2 (m, 2H).

【0111】〔製造例6〕

3-(3-シアノフェニル)-5-(アミノメチル)安息香酸メチルエステル

【0112】

【化22】



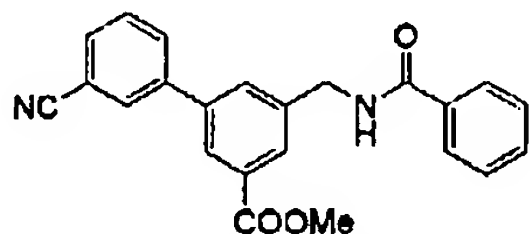
【0113】製造例5で得られた3-(3-シアノフェニル)-5-(プロモメチル)安息香酸メチルエステル 1.1 gをDMF 33 mLに溶かし、アジ化ナトリウム 325 mgをゆっくり加えた。反応液を室温下2時間攪拌した後、水80 mL、酢酸エチル120 mLを加えて有機物を抽出し、水層を酢酸エチル100 mLにて2回抽出した。抽出液を飽和食塩水で洗浄し、無水硫酸ナトリウム水溶液にて乾燥後、減圧下溶媒を留去して、淡黄色油状の3-(3-シアノフェニル)-5-(アジドメチル)安息香酸メチルエステルを粗生成物として得た。こうして得た3-(3-シアノフェニル)-5-(アジドメチル)安息香酸メチルエステルをフラスコに入れ、エタノール66 mLに溶解させ、パラジウム-炭酸バリウム1.1 gを加えた後、フラスコ内を水素で置換した。このまま室温にて6時間攪拌し、触媒をセライトろ過し、ろ液を濃縮した後、シリカゲルカラムクロマトグラフィーにて精製し、表題の目的物794 mgを得た(2段階の収率90%)。GC-MS (M-H) = 265

【0114】〔製造例7〕

3-(3-シアノフェニル)-5-ベンゾイルアミノメチル安息香酸メチルエステル

【0115】

【化23】



【0116】製造例6で得た化合物100 mgをクロロホルム0.7 mLに溶解した。この溶液に安息香クロリドの0.3 Mクロロホルム溶液1.5 mLを加え、攪拌しながらトリエチルアミンの0.3 Mクロロホルム溶液を加えて、室温にて2.5時間攪拌した。反応液にアミノメチルレジン(1.04 mmol/g) 200 mgを入れ、室温にて12時間攪拌し、グラスフィルターにて反応液をろ過し、ろ液に飽和炭酸水素ナトリウム水溶液1 mLを加え、分液し、抽出液を濃縮して目的物を得た。115 mg、収率84%。

MS = 371.0 (M+H)

この手法により、表1、表2に示す製造例1、2、3、4、5、15、16、17、18の前駆体であるニトリ

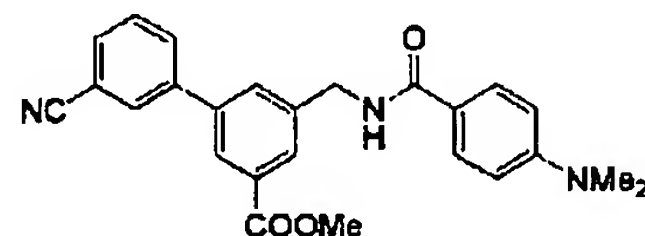
ル体を得た。

【0117】〔製造例8〕

3-(3-シアノフェニル)-5-(4-N, N-ジメチルアミノフェニルカルボニル)アミノメチル安息香酸メチルエステル

【0118】

【化24】



【0119】製造例6で得た化合物27 mgをクロロホルム2.0 mLに溶解した。4-N, N-ジメチルアミノ安息香酸21 mgを加え、さらにHOBt 27 mg、EDCI塩酸塩48 mgを加え、室温で終夜攪拌した。反応液をバリアン社製固相抽出用陽イオン交換樹脂カラムSCXならびに固相抽出用陰イオン交換樹脂カラムSAXに供し、不純物を除き、SCXに吸着された目的物を2規定アンモニアメタノール溶液で抽出した。抽出液を濃縮し、定量的に表題の化合物50 mgを得た。

MS (M+H) = 414.0

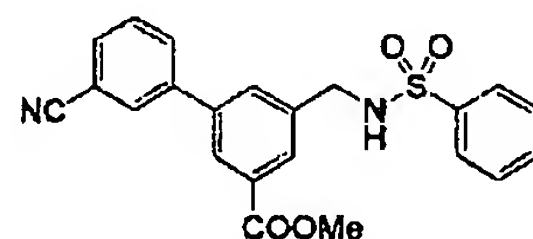
この手法により、製造例6、7、8、9、10、11、12、13、14、19、20、21、22、23、24、25、26、27、28、29、30、31、32の前駆体であるニトリル体を得た。

【0120】〔製造例9〕

3-(3-シアノフェニル)-5-ベンゼンスルホニルアミノメチル安息香酸メチルエステル

【0121】

【化25】



【0122】製造例6で得た化合物27 mgをクロロホルム0.5 mLに溶解した。この溶液にベンゼンスルホン酸クロリドの0.2 Mクロロホルム溶液0.6 mLを加え、攪拌しながらトリエチルアミンの0.2 Mクロロホルム溶液0.6 mLを加えて、室温にて12時間攪拌した。反応液にアミノメチルレジン(1.04 mmol/g) 200 mgを入れ、室温にて12時間攪拌し、グラスフィルターにて反応液をろ過し、ろ液に飽和炭酸水素ナトリウム水溶液1 mLを加え、分液し、抽出液を濃縮して定量的に目的物を得た。42 mg。

MS = 371.0 (M+H)

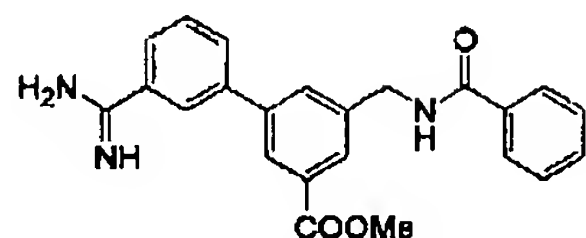
この手法により、表2に示す実施例33、34、35の前駆体であるニトリル体を得た。また、スルホン酸クロリド誘導体の代わりにイソシアナート誘導体を原料に用いて同様の操作を行うことにより、表5に示す製造例36、37、38の前駆体であるニトリル体を得た。

【0123】[実施例1]

3-(3-アミノフェニル)-5-ベンゾイルアミノ
メチルー安息香酸メチル

【0124】

【化26】



【0125】製造例7の化合物38mgをジクロロメタン60mlに溶解し、メタノール3.0mlを加えた。氷冷撹拌しながら塩化水素ガスを30分間吹き込んだ。0℃で30分間、室温で20時間撹拌した後、濃縮乾固した。飽和アンモニア-エタノール溶液30mlを加え、室温で5時間撹拌した後に濃縮した。得られた粗生成物をHPLC(ODS、溶出溶媒：水-メタノール)を用いて分取精製を行い、表題の目的物24mgを得た。60%。

MS=388.2 (M+H)

同様の手法により、表1、表2、表3、表4、表5に示す製造例2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24、25、26、2

7、28、29、30、31、32、33、34、35、36、37、38の化合物を合成した。

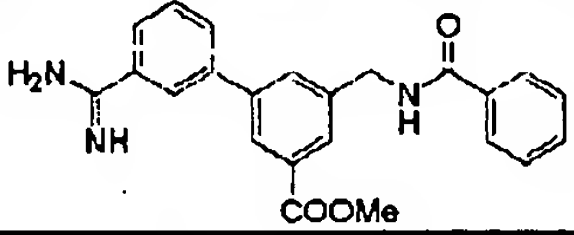
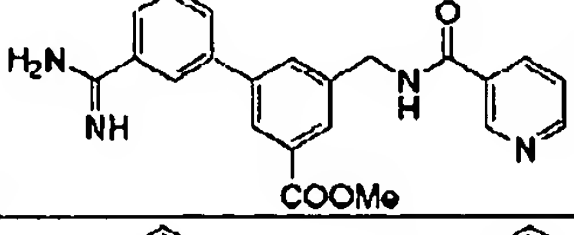
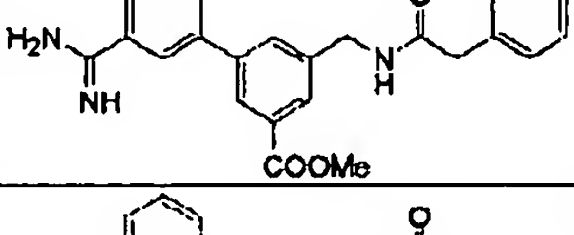
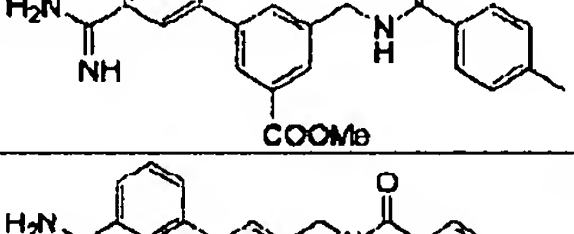
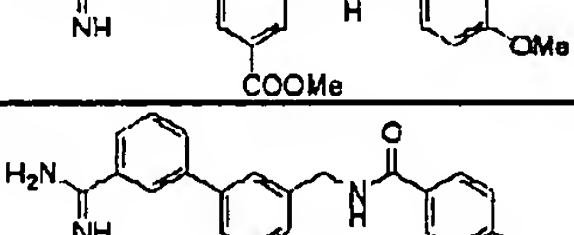
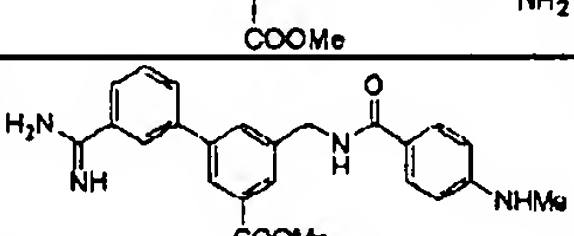
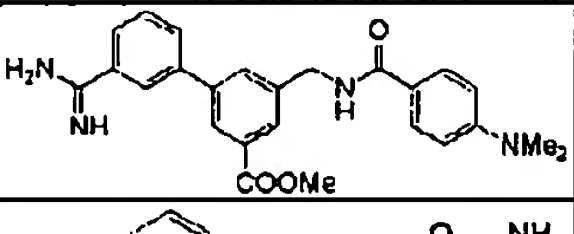
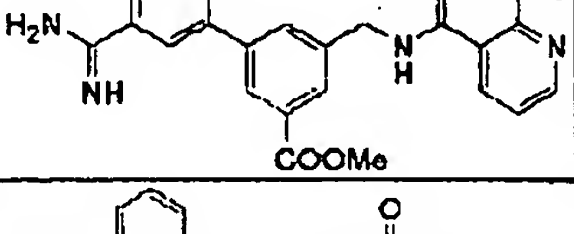
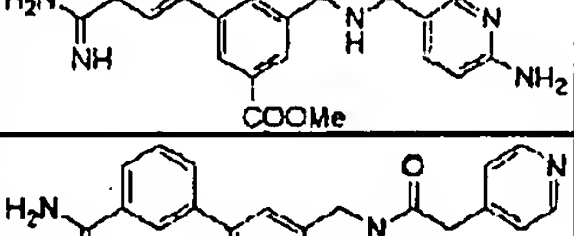
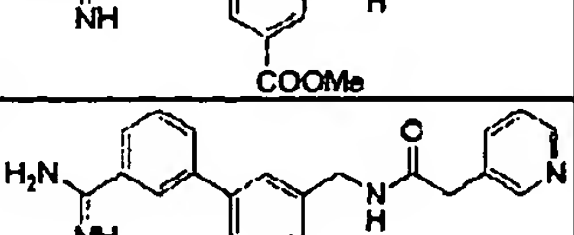
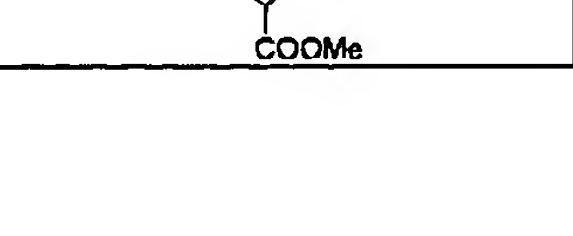

【0126】[実施例2]

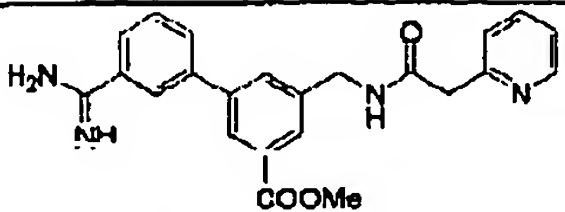
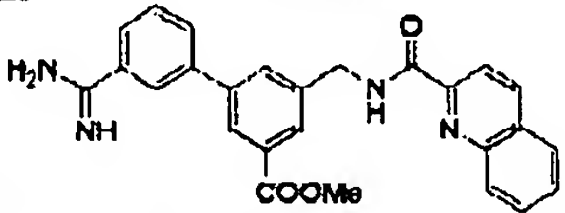
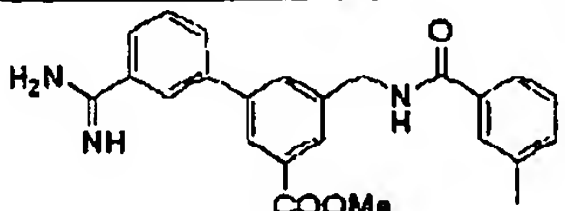
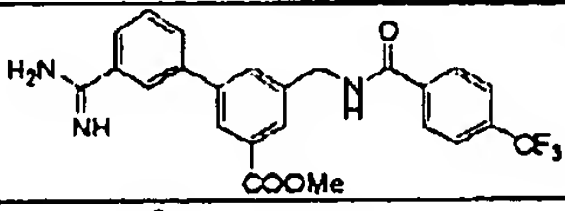
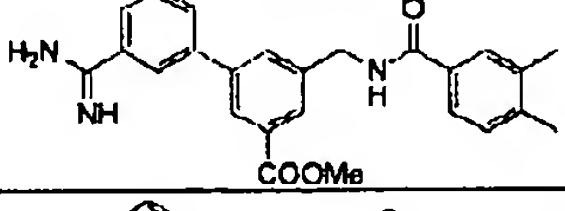
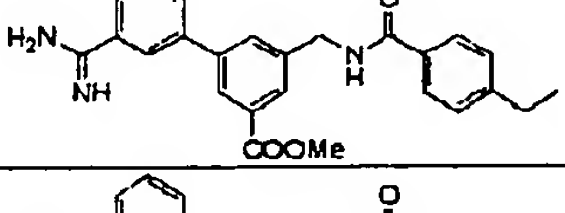
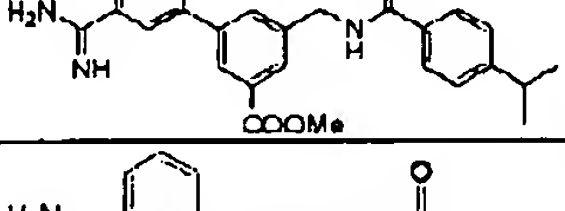
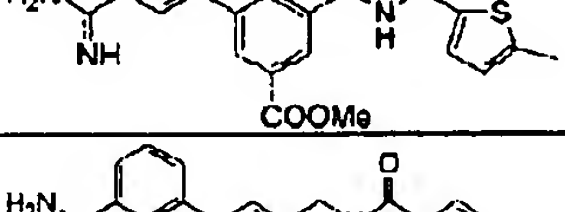
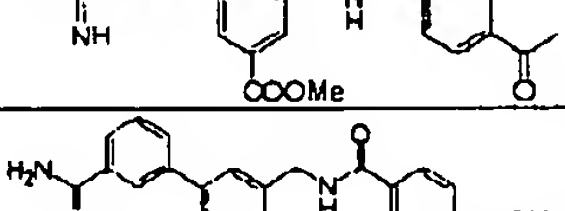
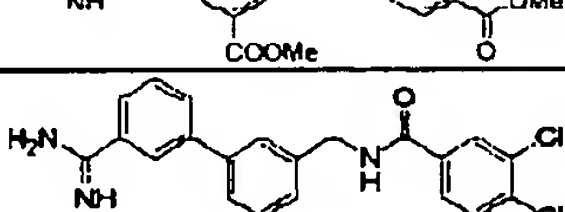
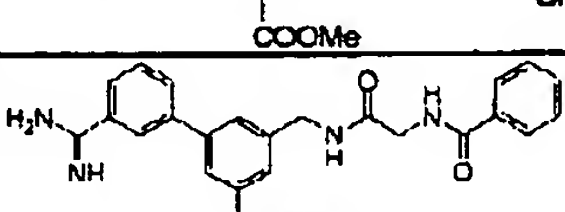
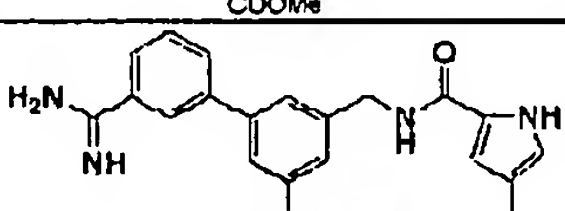
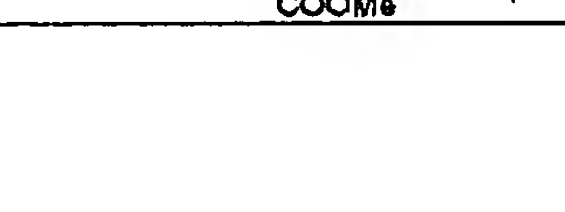
活性化血液凝固第X因子(FXa)阻害作用の測定

検体を水あるいは適当な濃度の有機溶媒(DMSOあるいはエタノールあるいはメタノール)を加えた水に溶解して検体とした。水で段階希釈した検体70μlに100mMトリス緩衝液(pH8.4)90μl、50mU/mlヒトFXa50mMトリス緩衝液(pH8.4)溶液20μl、2mM基質(第一化学S-2765)を添加し、30分間インキュベートした後50%酢酸50μlを加えて吸光度(A405)を測定した。FXaの代わりにトリス緩衝液を加えたものをブランクとし、検体の代わりに水を加えたものをコントロールとした。50%阻害活性(IC₅₀)を求め、FXa阻害作用の指標とした。その結果、製造例4、5、7、8、17、18、19の化合物にIC₅₀=0.1~1μM、製造例1、6、15、16、21、22、29の化合物にIC₅₀=1~10μMの阻害活性を認め、本発明によるビフェニルアミジン化合物がXa阻害剤であることが明らかとなった。

【0127】

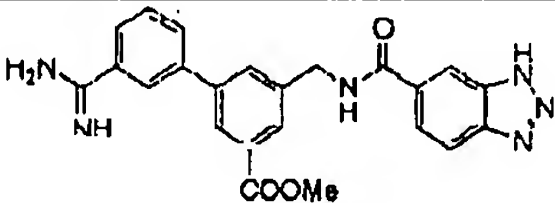
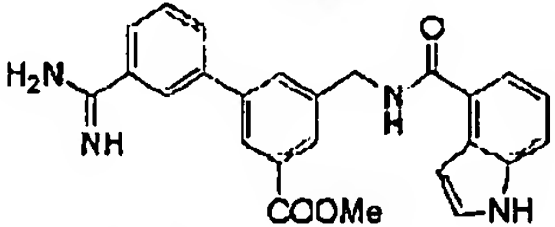
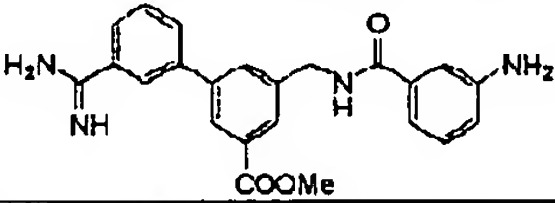
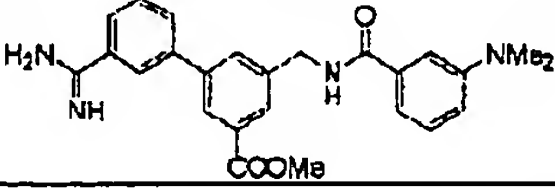
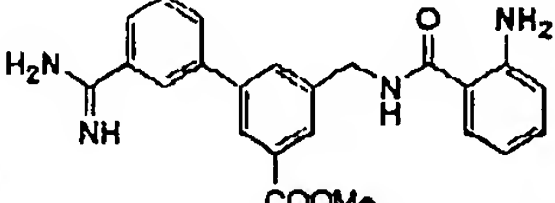
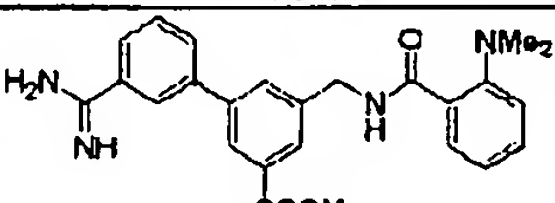
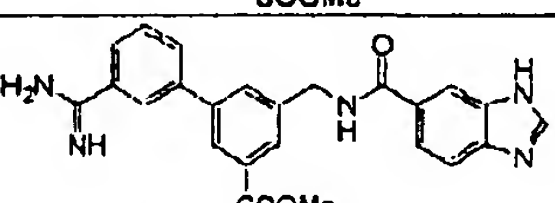
【表1】

製造例	構造	MSデータ
1		388.2 [M+H]
2		389.0 [M+H]
3		402.0 [M+H]
4		402.4 [M+H]
5		418.2 [M+H]
6		403.2 [M+H]
7		417.2 [M+H]
8		431.2 [M+H]
9		404.2 [M+H]
10		404.2 [M+H]
11		403.2 [M+H]
12		403.2 [M+H]

13		403.2 [M+H]
14		439.2 [M+H]
15		402.2 [M+H]
16		456.2 [M+H]
17		416.2 [M+H]
18		416.2 [M+H]
19		430.2 [M+H]
20		408.2 [M+H]
21		430.2 [M+H]
22		446.2 [M+H]
23		456.0 [M+H]
24		445.0 [M+H]
25		391.2 [M+H]

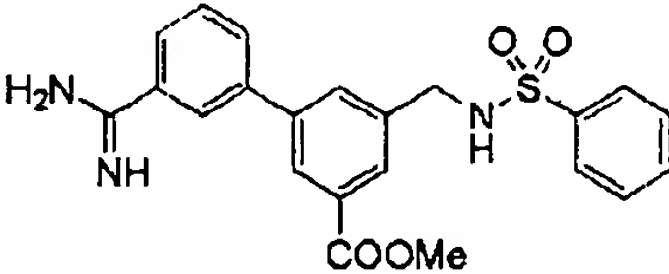
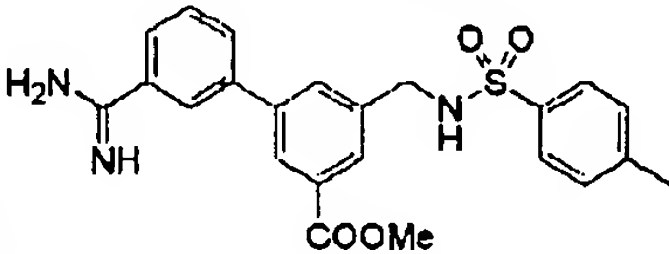
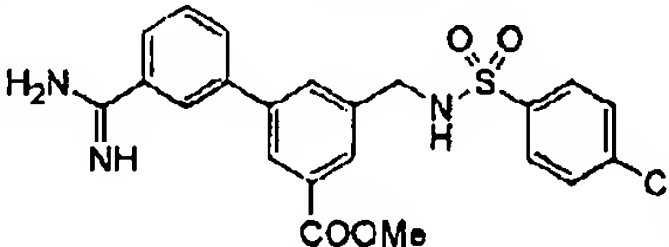
【0129】

【表3】

26		429.4 [M+H]
27		427.2 [M+H]
28		403.4 [M+H]
29		431.2 [M+H]
30		403.4 [M+H]
31		431.4 [M+H]
32		423.2 [M+H]

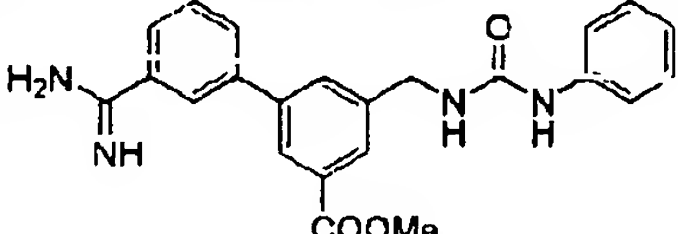
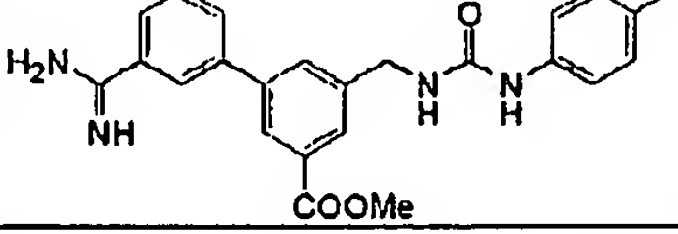
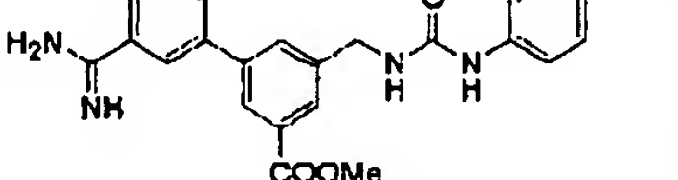
【0130】

【表4】

製造例	構造	MSデータ
33		24.0 [M+H]
34		438.0 [M+H]
35		453.2 [M+H]

【0131】

【表5】

製造例	構造	MSデータ
36		403.0 [M+H]
37		417.0 [M+H]
38		433.0 [M+H]

【0132】

【発明の効果】本発明のビフェニルアミジン誘導体またはその薬学的に許容される塩は、FXa活性を抑制する効果があり、FXa抑制剤として、心筋梗塞、脳血栓

症、末梢動脈血栓症、深部静脈血栓症等の血栓塞栓性疾患に対して臨床応用可能な予防剤および／または治療剤として使用することが可能であることが明らかとなった。

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(72)発明者 杉浦 聡	東京都日野市旭が丘4丁目3番2号 帝人株式会社東京研究センター内	Fターム(参考) 4C031 MA01	4C055 AA01 BA01 BA02 BA34 BA52 BB04 BB10 BB11 CA01 CA02 CA34 CA58 CB04 CB10 CB11 DA01 DA34 DB04 DB10 DB11
(72)発明者 中田 知久	東京都日野市旭が丘4丁目3番2号 帝人株式会社東京研究センター内	4C069 AC07 BA01 BB52	
(72)発明者 原 崇行	東京都日野市旭が丘4丁目3番2号 帝人株式会社東京研究センター内	4C086 AA01 AA02 AA03 BB02 BC05 BC14 BC17 BC29 BC39 BC61 MA01 MA02 MA03 MA04 MA05 NA14 ZA36 ZA54 ZC41	
(72)発明者 中井 康晴	東京都日野市旭が丘4丁目3番2号 帝人株式会社東京研究センター内	4C204 BB01 BB09 CB03 DB01 EB01 FB01 GB22	
(72)発明者 宝田 玲子	東京都日野市旭が丘4丁目3番2号 帝人株式会社東京研究センター内	4H006 AA01 AA03 AB24 AC30 AC52 AC53 AC59 AC61 BT32 BV72	

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(71)Applicant : **TEIJIN LTD**

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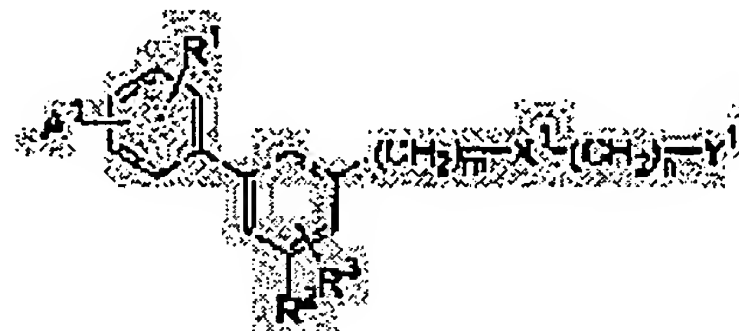
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NAKAI YASUHARU
TAKARADA REIKO

(54) BIPHENYLAMIDINE DERIVATIVE

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain the subject new compound clinically applicable and useful as a selective activated blood coagulation factor X (hereinafter abbreviated to Fxa) inhibitor.

SOLUTION: This biphenylamidine derivative is represented by formula I [A1 is amidino; R1 is H, F, Cl, Br, hydroxyl group, amino, nitro, a 1-10C alkyl or the like; R2 is F, Cl, Br, hydroxyl group, amino, a 1-10C



I

alkoxy or the like; R3 is H, F, Cl, Br, hydroxyl group, amino, nitro, a 1-10C alkyl or the like; X1 is NH-CO-NH or the like; Y1 is phenyl, naphthyl or the like; (m) is 1-3; (n) is 0-3], e.g. methyl 3-(3-amidinophenyl)-5-benzoylaminomethyl-benzoate. In the compound represented by formula I, a compound in which X1 is amide bond can be obtained by synthesizing a nitrile derivative which is a precursor using, e.g. a compound represented by formula II (R5 is H, a 1-10C alkyl or an aryl; R11 is F, Cl, Br or the like) and then carrying out the amidination reaction of the resultant nitrile derivative.

LEGAL STATUS

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[Date of final disposal for application]

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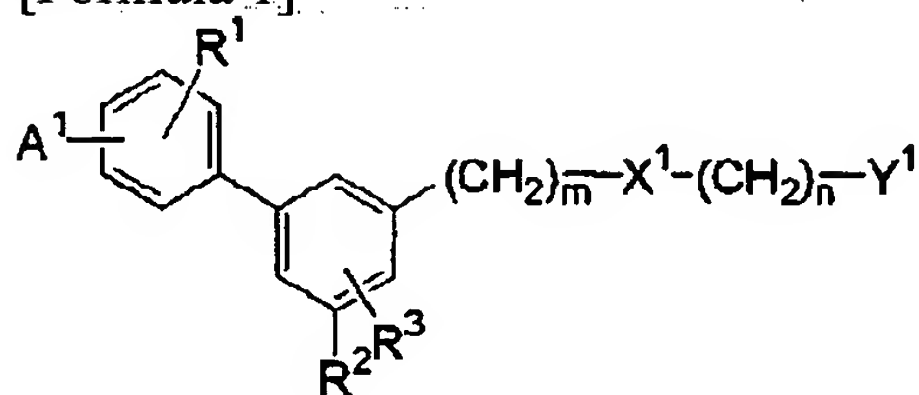
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CLAIMS

[Claim(s)]

[Claim 1] The following formula (1)

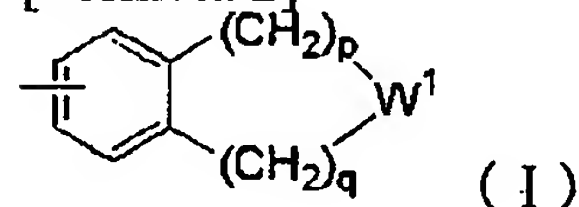
[Formula 1]



(1)

A1 expresses an amidino group among [formula (1)]. R1 A hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, the amino group, a nitro group, C1 - 10 alkyl groups, C1 - 10 alkoxy groups are expressed. or R2 A fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, the amino group, C1 - 10 alkoxy groups, A carboxyl group, C1 - 10 alkoxy carbonyl group, an aryloxy carbonyl group, an aralkoxy carbonyl machine, a carbamoyl group (the nitrogen atom which constitutes a carbamoyl group) it may be replaced by Monod, or G C1 - 10 alkyl groups, or the nitrogen atom of amino acid is sufficient C1 - 10 alkyl carbonyl group, C1 - 10 alkyl sulfenyl machine, C1 - 10 alkyl sulfinyl machine, C1 - 10 alkyl sulfonyl machine, Monod or G C1 - 10 alkylamino machine, Monod, or G C1 - 10 alkylamino sulfonyl machine, A sulfonic group, a phosphono machine, a screw (hydroxy carbonyl) methyl group, a screw (alkoxy carbonyl) methyl group, or 5-tetrazolyl group is expressed. R3 A hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, the amino group, a nitro group, C1 - 10 alkyl groups, C1 - 10 alkoxy groups, a carboxyl group, or C1 - 10 alkoxy carbonyl group is expressed. X1 Formula-NH-CO-NH-, -N(R4)-, -CO-N(R5)-, -N(R5)-CO-, -N(R5)-SO2-, -SO2-N (R5) - (R4 among a formula) expressing a hydrogen atom, C1 - 10 alkyl groups, C1 - 10 alkyl carbonyl group, and C1 - 10 alkyl sulfonyl machine, R5 expresses a hydrogen atom, C1 - 10 alkyl groups, and an aryl group Expressing the structure shown, Y1 is a phenyl group, a naphthyl group, or 1 - 2 **** aromatic heterocycle machine (these rings). A halogen atom, a hydroxyl group, C1 - 10 alkyl groups, C1 - 10 alkoxy groups, A trifluoromethyl machine, an aryl group, a methylene dioxy machine, C1 - 10 hydroxyalkyl machine, A carboxyl group, C1 - 4 alkoxy carbonyl group, C1 - 10 alkyl sulfenyl machine, C1 - 10 alkyl sulfinyl machine, C1 - 10 alkyl sulfonyl machine, you may have 1-3 substituents, such as Monod or a G alkylamino machine, 1-pyrrolidino machine, 1-piperidino machine, C1 - 10 amino alkyl group, Monod or a G alkylamino alkyl group, a sulfonic group, and a phosphono machine Or the following formula (I)

[Formula 2]

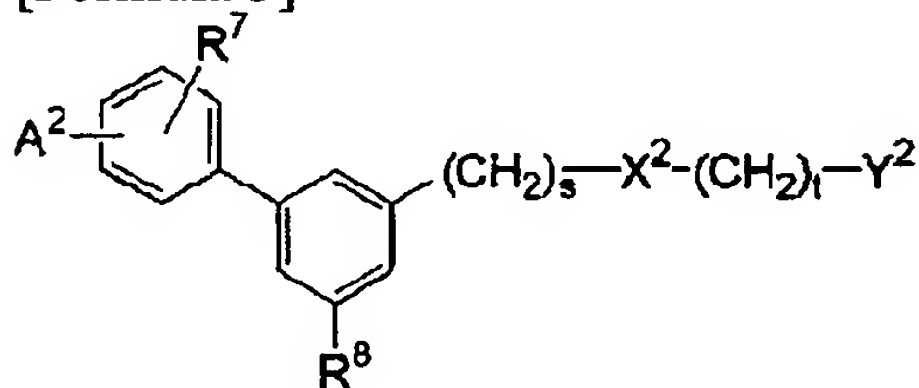


(I)

(The inside of a formula (I) and W1 are combination or formula-O-, -O-CO-, and -N(R6)- (R6 among a formula).) a hydrogen atom, C1 - 10 alkyl groups, C1 - 10 alkyl carbonyl group, C1 - 10 alkyl sulfonyl machine, or an aryl group is expressed expressing the structure shown, p and q express the integer of 0-3 which fill $4 \geq p+q \geq 2$ ($4 \geq p+q \geq$ when [however,] W1 shows combination 3) The basis shown or following formula-NH-CO-Z (the inside of a formula, ZC1 - 10 alkyl groups, or aryl group (the alkyl group or aryl group of the above and Z)) it may be replaced by C1 - 4 alkyl groups, a hydroxyl group, the amino group, Monod or a dialkylamino machine, the halogen atom, C1 - 4 alkoxy groups, the carboxyl group, and C1 - 4 alkoxy carbonyl group it expresses The basis shown is expressed, m expresses the integer of 1-3, and n is the integer (however, n is not 0 when Y1 is expressed with formula-NH-CO-Z.) of 0-3. it expresses] The biphenyl amidine derivative come out of and expressed, or its salt permitted pharmacologically.

[Claim 2] General formula (2)

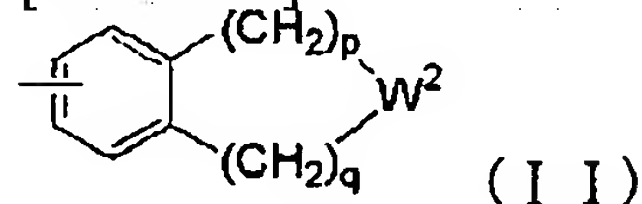
[Formula 3]



(2)

A2 expresses an amidino group among [formula (2). R7 A hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, the amino group, a nitro group, C1 - 4 alkyl groups, C1 - 4 alkoxy groups are expressed. or R8 A carboxyl group, C1 - 4 alkoxy carbonyl group, an aryloxy carbonyl group, an aralkoxy carbonyl machine, a carbamoyl group (the nitrogen atom which constitutes a carbamoyl group) it may be replaced by Monod or G C1 - 4 alkyl groups, or the nitrogen atom of amino acid is sufficient It expresses and X2 expresses the structure shown by formula-NH-, -NH-CO-, -NH-SO₂-, and -NH-CO-NH-. Y2 A phenyl group, a naphthyl group, or 1 - 2 **** aromatic heterocycle machine (these rings) A halogen atom, a hydroxyl group, C1 - 4 alkyl groups, C1 - 4 alkoxy groups, A trifluoromethyl machine, an aryl group, a methylene dioxy machine, C1 - 4 hydroxyalkyl machine, A carboxyl group, C1 - 4 alkoxy carbonyl group, C1 - 4 alkyl sulfinyl machine, you may have C1 - 4 alkyl sulfinyl machine, C1 - 4 alkyl sulfonyl machine, Monod or a G alkylamino machine, 1-pyrrolidino machine, 1-piperidino machine, C1 - 4 amino alkyl group, Monod, or 1-3 G alkylamino alkyl groups Or the following formula (II)

[Formula 4]

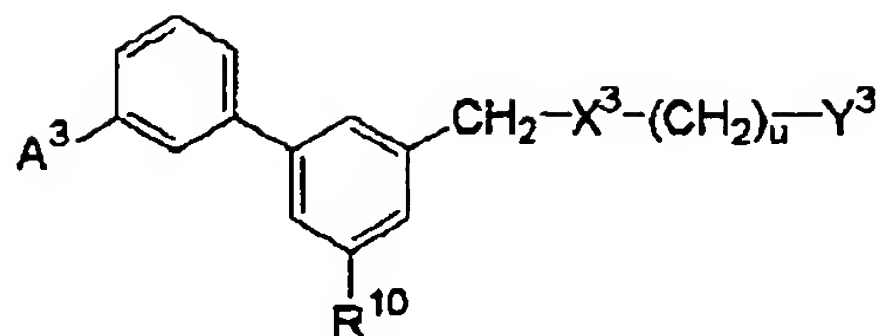


(I I)

(The inside of a formula (II) and W2 are combination or formula-O-, and -N(R9)- (R9 among a formula).) a hydrogen atom, C1 - 10 alkyl groups, C1 - 10 alkyl carbonyl group, C1 - 10 alkyl sulfonyl machine, or an aryl group is expressed expressing the structure shown, p and q express the integer of 0-3 which fill $4 \geq p+q \geq 2$ ($4 \geq p+q \geq$ when [however,] W1 shows combination 3) The basis shown or following formula-NH-CO-Z (the inside of a formula, ZC1 - 10 alkyl groups, or aryl group (the alkyl group or aryl group of the above and Z)) it may be replaced by C1 - 4 alkyl groups, a hydroxyl group, the amino group, Monod or a dialkylamino machine, the halogen atom, C1 - 4 alkoxy groups, the carboxyl group, and C1 - 4 alkoxy carbonyl group it expresses The basis shown is expressed, s expresses the integer of 1-2, and t is the integer (however, t is not 0 when Y2 is expressed with formula:-NH-CO-Z.) of 0-2. it expresses] The biphenyl amidine derivative come out of and expressed, or its salt permitted pharmacologically.

[Claim 3] General formula (3)

[Formula 5]



(3)

A³ expresses an amidino group among [formula (3)]. R¹⁰ A carboxyl group, C1 - 4 alkoxy carbonyl group, an aryloxy carbonyl group, an aralkoxy carbonyl machine, a carbamoyl group (the nitrogen atom which constitutes a carbamoyl group) it may be replaced by Monod or G C1 - 4 alkyl groups, or the nitrogen atom of amino acid is sufficient It expresses and X³ expresses the structure shown by formula-NH-, -NH-CO-, -NH-SO₂-, and -NH-CO-NH-. Y³ A phenyl group, a naphthyl group, or 1 - 2 **** aromatic heterocycle machine (these rings) A halogen atom, a hydroxyl group, C1 - 4 alkyl groups, C1 - 4 alkoxy groups, A trifluoromethyl machine, a methylene dioxy machine, C1 - 4 hydroxyalkyl machine, you may have a carboxyl group, C1 - 4 alkoxy carbonyl group, Monod or a G alkylamino machine, 1-pyrrolidino machine, 1-piperidino machine, C1 - 4 amino alkyl group, Monod, or 1-3 G alkylamino alkyl groups Or following formula-NH-CO-Z (the inside of a formula, ZC1 - 10 alkyl groups, or aryl group (the alkyl group or aryl group of the above and Z)) it may be replaced by C1 - 4 alkyl groups, a hydroxyl group, the amino group, Monod or a dialkylamino machine, the halogen atom, C1 - 4 alkoxy groups, the carboxyl group, and C1 - 4 alkoxy carbonyl group it expresses Expressing the basis shown, u is the integer (however, u is not 0 when Y³ is expressed with formula-NH-CO-Z.) of 0-1. it expresses] The biphenyl amidine derivative come out of and expressed, or its salt permitted pharmacologically.

[Claim 4] A biphenyl amidine derivative or its salt permitted pharmacologically the claim 1 to which X³ of the above-mentioned formula (3) is expressed with formula-NH-CO-, -NH-SO₂-, and -NH-CO-NH- - given in 3 any 1 terms.

[Claim 5] A biphenyl amidine derivative or its salt permitted pharmacologically the claim 1 to which X³ of the above-mentioned formula (3) is expressed with formula-NH- - given in 3 any 1 terms.

[Claim 6] The prodrug object which generates a biphenyl amidine derivative a claim 1 - given in 5 any 1 terms, or its salt permitted pharmacologically in the living body.

[Claim 7] The blood coagulation inhibitor which consists of a compound a claim 1 - given in 6 any 1 terms or its salt permitted pharmacologically, and support permitted pharmacologically at least.

[Claim 8] The preventive of the thrombus which consists of a compound a claim 1 - given in 6 any 1 terms or its salt permitted pharmacologically, and support permitted pharmacologically at least, or a plug.

[Claim 9] The treatment agent of the thrombus or plug which consists of a compound a claim 1 - given in 6 any 1 terms or its salt permitted pharmacologically, and support permitted pharmacologically at least.

[Translation done.]

DETAILED DESCRIPTION

JP 2000-178243

* NOTICES *

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1. This document has been translated by computer. So the translation may not reflect the original precisely.
2. **** shows the word which can not be translated.
3. In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[The technical field to which invention belongs] this invention relates to the new alternative Xth factor (it omits Following FXa) inhibitor of activation blood coagulation shown by the formula (1).

[0002]

[Description of the Prior Art] Anticoagulant therapy is bearing the role important as medical treatment and a prophylaxis to thrombus plug nature disorders, such as myocardial infarction, cerebral thrombosis, peripheral artery thrombosis, and deep venous thrombosis.

[0003] In prevention of chronic thrombosis, the safe and suitable oral anticoagulant in which prolonged administration is possible is especially required. However, in the present condition, a walfarin potassium with difficult control of anticoagulation ability only exists, and the anticoagulant which is easier to use is called for.

[0004] It was known that there is a danger that an antithrombin agent will cause a bleeding inclination as a side effect which is looked at by the hirudine, for example although development is furthered as an anticoagulant from the former. It is becoming clear that suppression of FXa located in the upstream of a thrombin in a blood coagulation cascade is more efficient than suppression of a thrombin in mechanism, and such a side effect is weak in a FXa inhibitor, and it is clinically desirable.

[0005] the biphenyl amidine compound in which FXa prevention activity is shown -- the 17th May Day SHINARU chemistry symposium, the collection of the 6th physic chemistry sectional meeting annual convention summaries, and 184- it is indicated by 185 and 1997 However, this invention compound is a new compound which is clearly different on structure in that the hetero atom is utilized for combination with the cyclic structure which will interact with the biphenyl amidine structure which will interact with S1 pocket, and the aryl joint site.

[0006] Moreover, although the annular imino derivative (JP,4-264068,A) is indicating the biphenyl amidine derivative, this inventions differ clearly at the point which is carrying out combination by the hetero atom with the benzylic position.

[0007]

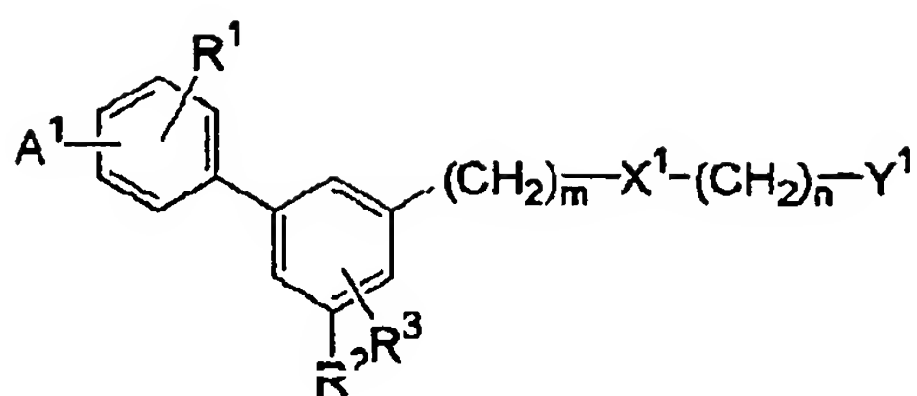
[Problem(s) to be Solved by the Invention] The purpose of this invention is offering the new compound which may serve as a FXa inhibitor in which clinical application is possible.

[0008]

[Means for Solving the Problem] This invention persons are the following formulas (1), as a result of repeating examination wholeheartedly, in order to attain the above-mentioned purpose.

[0009]

[Formula 6]

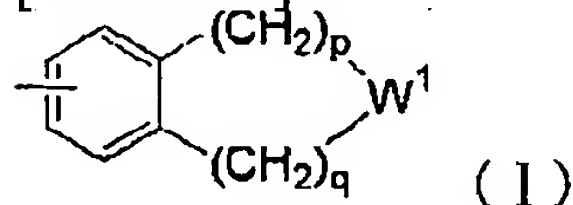


(1)

[0010] A1 expresses an amidino group among [formula (1)]. R1 A hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, the amino group, a nitro group, C1 - 10 alkyl groups, C1 - 10 alkoxy groups are expressed. or R2 A fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, the amino group, C1 - 10 alkoxy groups, A carboxyl group, C1 - 10 alkoxy carbonyl group, an aryloxy carbonyl group, an aralkoxy carbonyl machine, a carbamoyl group (the nitrogen atom which constitutes a carbamoyl group) it may be replaced by Monod, or G C1 - 10 alkyl groups, or the nitrogen atom of amino acid is sufficient C1 - 10 alkyl carbonyl group, C1 - 10 alkyl sulfenyl machine, C1 - 10 alkyl sulfinyl machine, C1 - 10 alkyl sulfonyl machine, Monod or G C1 - 10 alkylamino machine, Monod, or G C1 - 10 alkylamino sulfonyl machine, A sulfonic group, a phosphono machine, a screw (hydroxy carbonyl) methyl group, a screw (alkoxy carbonyl) methyl group, or 5-tetrazolyl group is expressed. R3 A hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, the amino group, a nitro group, C1 - 10 alkyl groups, C1 - 10 alkoxy groups, a carboxyl group, or C1 - 10 alkoxy carbonyl group is expressed. X1 Formula-NH-CO-NH-, -N(R4)-, -CO-N(R5)-, -N(R5)-CO-, -N(R5)-SO2-, -SO2-N (R5) - (R4 among a formula) expressing a hydrogen atom, C1 - 10 alkyl groups, C1 - 10 alkyl carbonyl group, and C1 - 10 alkyl sulfonyl machine, R5 expresses a hydrogen atom, C1 - 10 alkyl groups, and an aryl group Expressing, Y1 is a phenyl group, a naphthyl group, or 1 - 2 **** aromatic heterocycle machine (these rings). A halogen atom, a hydroxyl group, C1 - 10 alkyl groups, C1 - 10 alkoxy groups, A trifluoromethyl machine, an aryl group, a methylene dioxy machine, C1 - 10 hydroxyalkyl machine, A carboxyl group, C1 - 4 alkoxy carbonyl group, C1 - 10 alkyl sulfenyl machine, C1 - 10 alkyl sulfinyl machine, C1 - 10 alkyl sulfonyl machine, you may have 1-3 substituents, such as Monod or a G alkylamino machine, 1-pyrrolidino machine, 1-piperidino machine, C1 - 10 amino alkyl group, Monod or a G alkylamino alkyl group, a sulfonic group, and a phosphono machine Or the following formula (I)

[0011]

[Formula 7]



(1)

[0012] (The inside of a formula (I) and W1 are combination or formula-O-, -O-CO-, and -N(R6)- (R6 among a formula).) a hydrogen atom, C1 - 10 alkyl groups, C1 - 10 alkyl carbonyl group, C1 - 10 alkyl sulfonyl machine, or an aryl group is expressed expressing the structure shown, p and q express the integer of 0-3 which fill 4 $\geq p+q \geq 2$ (4 $\geq p+q \geq$ when [however,] W1 shows combination 3) The basis shown or following formula-NH-CO-Z (the inside of a formula, ZC1 - 10 alkyl groups, or aryl group (the alkyl group or aryl group of the above and Z)) it may be replaced by C1 - 4 alkyl groups, a hydroxyl group, the amino group, Monod or a dialkylamino machine, the halogen atom, C1 - 4 alkoxy groups, the carboxyl group, and C1 - 4 alkoxy carbonyl group it expresses The basis shown is expressed, m expresses the integer of 1-3, and n is the integer (however, n is not 0 when Y1 is expressed with formula:-NH-CO-Z1.) of 0-3. it expresses] Come out, the biphenyl amidine derivative expressed or its salt permitted pharmacologically is found out, and it comes to complete this invention.

[0013] Hereafter, this invention is explained in detail. In the above-mentioned definition to the substituent of the compound of the formula in this specification (1), a formula (2), or a formula (3) with "C1 - 4 alkyl groups" The shape of a straight chain which has 1-4 carbon numbers, the letter of branching, or an annular hydrocarbon group is meant. For example, a methyl group, an ethyl group, a

propyl group, an isopropyl machine, a butyl, an isobutyl machine, a tert-butyl, a cyclo propyl group, etc. are expressed, and a methyl group, an ethyl group, a propyl group, and an isopropyl machine are desirable especially.

[0014] The shape of a straight chain which has 1-10 carbon numbers with "C1 - 10 alkyl groups", The letter of branching or an annular hydrocarbon group is meant. For example, a methyl group, an ethyl group, A propyl group, an isopropyl machine, a butyl, an isobutyl machine, a tert-butyl, A pentyl machine, a neopentyl machine, an isopentyl machine, 1, 2-dimethyl propyl group, Hexyl machine, iso hexyl machine, 1, and 1-dimethyl butyl, 2, and 2-dimethyl butyl, 1-ethyl butyl, 2-ethyl butyl, a heptyl machine, an iso heptyl machine, 1-methyl hexyl, 2-methyl hexyl, an octyl machine, a 2-ethylhexyl machine, A nonyl machine, a decyl group or 1-methyl nonyl machine, a cyclo propyl group, A cyclo butyl, a cyclopentyl group, a cyclohexyl machine, a cycloheptyl machine, A cyclo octyl machine, an adamantyl machine, etc. are expressed. especially A methyl group, an ethyl group, A propyl group, an isopropyl machine, a butyl, a tert-butyl, and a cyclohexyl machine are desirable, and especially when it is the substituent contained especially in substituents Y1 and Y2 or Y3, a methyl group, an ethyl group, and an isopropyl machine are desirable.

[0015] Specifically, an "aryl group" means ring machines, such as a phenyl group, a naphthyl group, a thiophenyl machine, and a pyridyl machine, and is a phenyl group and a naphthyl group preferably.

[0016] Specifically, a benzyl, a phenethyl machine, a phenylpropyl machine, 1-naphthyl methyl group, 2-naphthyl methyl group, etc. are mentioned, and an "aralkyl machine" is a benzyl preferably.

[0017] The carbonyl group which has ** with the straight chain of 1-4 carbon numbers, the letter of branching, or an annular alkyl side chain as "C1 - a 4 alkyl carbonyl group" is expressed, for example, a formyl machine, an acetyl group, a propionyl machine, a butyryl machine, an isobutyryl machine, a pivaloyl machine, etc. are meant, and they are the acetyl group of 1-3 carbon numbers, and a propionyl machine preferably.

[0018] As "C1 - a 10 alkyl carbonyl group" A carbonyl group with the straight chain, the letter of branching, or the annular chain which has 1-10 carbon numbers is expressed. For example, a formyl machine, an acetyl group, a pro PIONIORU machine, a butyryl machine, an isobutyryl machine, A valeryl machine, an iso valeryl machine, a pivaloyl machine, a hexa noil machine, a HEPUTA noil machine, An octanoyl group, a nonanoyl machine, a cyclopentyl carbonyl group, a cyclohexyl carbonyl group, etc. are meant, and they are the acetyl group of 1-8 carbon numbers, a propionyl machine, a butyryl machine, a hexa noil machine, and an octanoyl group preferably.

[0019] A "aryl carbonyl group" means a benzoyl, 4-methoxy benzoyl, 3-trifluoromethyl benzoyl, or the carbonyl group that the heterocycle combined, and is a benzoyl preferably.

[0020] An "aryloxy carbonyl group" means a phenoxy carbonyl group, a naphthyloxy carbonyl group, 4-methylphenoxy carbonyl group, 3-chloro phenoxy carbonyl group, 4-methoxy phenoxy carbonyl group, or an indan-5-yloxy carbonyl group, and is a phenoxy carbonyl group and an indan-5-yloxy carbonyl group preferably.

[0021] An "aralkoxy carbonyl machine" means a benzyloxycarbonyl machine, 4-methoxybenzyloxy carbonyl group, 3-trifluoromethyl benzyloxycarbonyl machine, a 3-OKISOHIDOROISO benzofuranyl oxy-carbonyl group, etc., and is a benzyloxycarbonyl machine and a 3-OKISOHIDOROISO benzofuranyl oxy-carbonyl group preferably.

[0022] With "C1 - 4 alkoxy carbonyl group", a methoxycarbonyl group, An ethoxycarbonyl machine, a propoxy carbonyl group, an isopropoxy carbonyl group, A butoxycarbonyl machine, an iso butoxycarbonyl machine, and a sec-butoxycarbonyl machine, The carbonyl group replaced by the alkoxy group of the carbon numbers 1-4, such as a tert-butoxycarbonyl machine and an acetoxymachine, is meant. preferably It is a methoxycarbonyl group and an ethoxycarbonyl machine, and when it is the substituent contained especially in substituents Y1 and Y2 or Y3, a methoxycarbonyl group and an ethoxycarbonyl machine are desirable.

[0023] With "C1 - 10 alkoxy carbonyl group" A methoxycarbonyl group, an ethoxycarbonyl machine, a propoxy carbonyl group, An isopropoxy carbonyl group, a butoxycarbonyl machine, an iso butoxycarbonyl machine, A sec-butoxycarbonyl machine, a tert-butoxycarbonyl machine, A pentyloxy

carbonyl group, an isopentyloxy carbonyl group, a neopentyl oxy-carbonyl group, A hexyloxy carbonyl group, a heptyloxy carbonyl group, an octyloxy carbonyl group, Or an acetoxy machine, a pivaloyloxy machine, Or 5-methyl-3-oxo -The methoxycarbonyl group replaced by the alkoxy group of the carbon numbers 1-10, such as 2 and 4-dioxo RENIRU machine, is meant. preferably A methoxycarbonyl group, an ethoxycarbonyl machine, a propoxy carbonyl group, An isopropoxy carbonyl group, an acetoxy methyloxy carbonyl group, A pivaloyloxymethyloxy carbonyl group, a methyloxy (5-methyl-3-oxo-2, 4-dioxo nil) carbonyl group, When it is an ethoxycarbonyloxy ethyloxy carbonyl group and is the substituent contained especially in substituents Y1 and Y2 or Y3, a methoxycarbonyl group and an ethoxycarbonyl machine are desirable.

[0024] "C1 - 4 alkoxy groups" mean the alkoxy group which has 1-4 carbon numbers, and are specifically a methoxy machine, an ethoxy basis, a propoxy group, an isopropoxy group, a butoxy machine, an iso butoxy machine, a sec-butoxy machine, a tert-butoxy machine, etc., a methoxy machine, an ethoxy basis, and an isopropyl machine are desirable especially, and when it is the substituent contained especially in substituents Y1 and Y2 or Y3, a methoxy machine and an ethoxy basis are

[0025] "C1 - 10 alkoxy groups" mean the alkoxy group which has 1-10 carbon numbers. Specifically A methoxy machine, an ethoxy basis, a propoxy group, an isopropoxy group, A butoxy machine, an iso butoxy machine, a sec-butoxy machine, a tert-butoxy machine, A pentyloxy machine, a neopentyl oxy-basis, and a tert-pentyloxy machine, 2-methyl butoxy machine, a hexyloxy machine, an iso hexyloxy machine, A heptyloxy machine, an iso heptyloxy machine, an octyloxy machine, an iso octyloxy machine, It is a cyclohexyloxy machine etc., the methoxy machine of 1-6 carbon numbers, an ethoxy basis, and a cyclohexyl machine are desirable especially, and when it is the substituent contained especially in substituents Y1 and Y2 or Y3, a methoxy machine and an ethoxy basis are desirable.

[0026] "C1 - 4 alkyl sulfenyl machine" mean the alkyl sulfenyl machine which has 1-4 carbon numbers, specifically express a methylthio machine, an ethyl thio machine, a butyl thio machine, an isobutyl thio machine, etc., and are a methylthio machine preferably.

[0027] "C1 - 10 alkyl sulfenyl machine" mean the alkyl sulfenyl machine which has 1-10 carbon numbers, specifically express a methylthio machine, an ethyl thio machine, a butyl thio machine, an isobutyl thio machine, a pentyl thio machine, a hexyl thio machine, a heptyl thio machine, an octyl thio machine, etc., and are a methylthio machine preferably.

[0028] "C1 - 4 alkyl sulfinyl machine" mean the alkyl sulfinyl machine which has 1-4 carbon numbers, specifically express a methyl sulfinyl machine, an ethyl sulfinyl machine, a butyl sulfinyl machine, etc., and are a methyl sulfinyl machine preferably.

[0029] "C1 - 10 alkyl sulfinyl machine" mean the alkyl sulfinyl machine which has 1-10 carbon numbers, specifically express a methyl sulfinyl machine, an ethyl sulfinyl machine, a butyl sulfinyl machine, a hexyl sulfinyl machine, an octyl sulfinyl machine, etc., and are a methyl sulfinyl machine preferably.

[0030] "C1 - 4 alkyl sulfonyl machine" mean the alkyl sulfonyl machine which has 1-4 carbon numbers, are specifically a methyl sulfonyl machine, an ethyl sulfonyl machine, and a butyl sulfonyl machine, and are a methyl sulfonyl machine preferably.

[0031] "C1 - 10 alkyl sulfonyl machine" mean the alkyl sulfonyl machine which has 1-10 carbon numbers. Specifically A methyl sulfonyl machine, an ethyl sulfonyl machine, a propyl sulfonyl machine, An isopropyl sulfonyl machine, a butyl sulfonyl machine, an isobutyl sulfonyl machine, A pentyl sulfonyl machine, an isopentyl sulfonyl machine, a neopentyl sulfonyl machine, A hexyl sulfonyl machine, a heptyl sulfonyl machine, an octyl sulfonyl machine, A nonyl sulfonyl machine, a desyl sulfonyl machine, a cyclohexyl sulfonyl machine, etc. are expressed, and the methyl sulfonyl machine of 1-8 carbon numbers, an ethyl sulfonyl machine, a butyl sulfonyl machine, a hexyl sulfonyl machine, and especially an octyl sulfonyl machine are desirable especially.

[0032] With "Monod or a G alkylamino machine" A methylamino machine, a dimethylamino machine, an ethylamino machine, a propylamino machine, A diethylamino machine, an isopropylamino machine, a diisopropylamino machine, A dibutylamino machine, a butylamino machine, the isobutyl amino group, and a sec-butylamino machine, A tert-butylamino machine, a pentylamino machine, a

hexylamino machine, The heptyl amino group, the octyl amino group, a cyclopentylamino machine, a cyclohexylamino machine, etc. are meant. It is a methylamino machine, a dimethylamino machine, an ethylamino machine, a diethylamino machine, and a propylamino machine preferably, and especially when it is the substituent contained especially in substituents Y1 and Y2 or Y3, a dimethylamino machine and a diethylamino machine are desirable.

[0033] "Monod contained in substituents Y1 and Y2 or Y3 -- or With a G alkylamino alkyl group", specifically A methylamino methyl group, A dimethyl aminomethyl machine, a diethyl aminomethyl machine, a methylamino ethyl group, A dimethylaminoethyl machine, an ethylamino ethyl group, a diethylaminoethyl machine, A methylaminopropyl machine, a dimethylamino propyl group, an ethylaminopropyl machine, A diethylamino propyl group, a methylamino butyl, a dimethylamino butyl, etc. are meant, and they are a dimethyl aminomethyl machine, a diethyl aminomethyl machine, and a diethylaminoethyl machine preferably.

[0034] Substituents Y1 and Y2, or "C1 - 4 amino alkyl group" contained in Y3 expresses the alkyl group of the carbon numbers 1-4 replaced by the amino group, specifically means an aminomethyl machine, 1-aminoethyl machine, 2-aminoethyl machine, 1-aminopropyl machine, 2-aminopropyl machine, 3-aminopropyl machine, etc., and are an aminomethyl machine, 1-aminomethyl machine, 2-aminoethyl machine, and 1-aminopropyl machine preferably.

[0035] With "Monod or a G alkylamino sulfonyl machine" Specifically A methylamino sulfonyl machine, a dimethylamino sulfonyl machine, An ethylamino sulfonyl machine, a propylamino sulfonyl machine, a diethylamino sulfonyl machine, An isopropylamino sulfonyl machine, a diisopropylamino sulfonyl machine, A dibutylamino sulfonyl machine, a butylamino sulfonyl machine, an isobutyl amino sulfonyl machine, A sec-butylamino sulfonyl machine, a tert-butylamino sulfonyl machine, A pentylamino sulfonyl machine, a hexylamino sulfonyl machine, a heptyl amino sulfonyl machine, An octyl amino sulfonyl machine etc. is meant. preferably A methylamino sulfonyl machine, It is a dimethylamino sulfonyl machine, an ethylamino sulfonyl machine, a diethylamino sulfonyl machine, and a propylamino sulfonyl machine, and they are a methylamino sulfonyl machine and a dimethylamino sulfonyl machine still more preferably.

[0036] A screw (methoxycarbonyl) methyl group, a screw (ethoxycarbonyl) methyl group, etc. are specifically expressed as a "screw (alkoxy carbonyl) methyl group", and it is a screw (methoxycarbonyl) methyl group preferably.

[0037] "C1 - 4 hydroxyalkyl machine" express the alkyl group of the carbon numbers 1-4 replaced by the hydroxyl. Specifically A hydroxymethyl group, 1-hydroxyethyl machine, 2-aminoethyl machine, 1-hydroxypropyl machine, 2-hydroxypropyl machine, 3-hydroxypropyl machine, etc. are meant. preferably It is a hydroxymethyl group, 1-hydroxyethyl machine, 2-hydroxyethyl machine, and 1-hydroxypropyl machine, and a hydroxymethyl group is desirable when it is the substituent contained especially in substituents Y1 and Y2 or Y3.

[0038] With substituents Y1 and Y2 or "1 - 2 **** aromatic heterocycle" contained in Y3 1 which has an oxygen atom, a sulfur atom, and/or 1-3 nitrogen atoms as a hetero atom - 2 **** aromatic heterocycle are meant. Specifically A furan ring, a thiophene ring, a pyrrole ring, a pyridine ring, a pyrazine ring, An imidazole ring, a triazole ring, an oxazole ring, an isoxazole ring, A thiazole ring, a thiadiazole ring, the Indore ring, a benzimidazole ring, They are a bends triazole ring, a quinoline ring, an isoquinoline ring, a benzofuran ring, and a bends thiophene ring. as the suitable example A thiophene ring, a thiazole ring, a pyrrole ring, a pyridine ring, the Indore ring, an imidazole ring, a triazole ring, a benzimidazole ring, and a quinoline ring are mentioned.

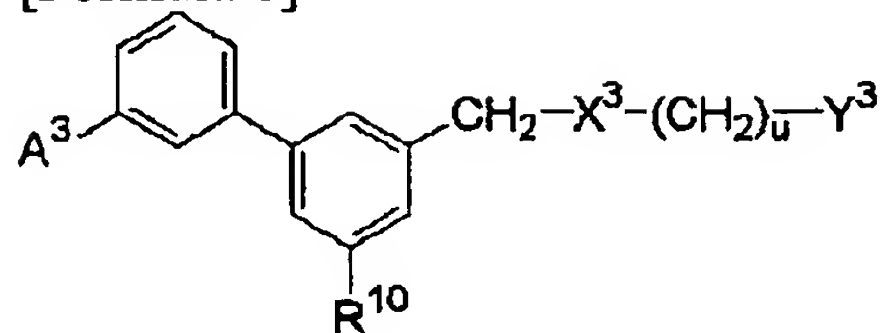
[0039] this invention compound (1) may form an acid addition salt. Moreover, a salt with a base may be formed depending on the kind of substituent. Although it will not be limited especially if such a salt is a salt permissible in physic Specifically A hydrochloride, the hydrobromate, hydrogen iodide acid chloride, phosphate, a nitrate, Mineral-acid salts, such as a sulfate; Methanesulfon acid chloride, a 2-hydroxy ethane-sulfonic-acid salt, Organic sulfonates [, such as a p-toluenesulfonic-acid salt,]; and acetate, a trifluoroacetic-acid salt, A propionate, an oxalate, chestnut acid chloride, the succinate, a glutarate, Organic carboxylates, such as an adipate, a tartrate, a maleate, a malate, and a mandelic-acid

salt, are contained as an acid addition salt. A salt with organic bases, such as a salt with inorganic bases, such as sodium salt, potassium salt, magnesium salt, a calcium salt, and an aluminum salt, and a monomethylamine salt, an ethylamine salt, a lysine salt, an ornithine salt, is mentioned as a salt with a base.

[0040] The desirable range of the compound of this invention is the following formula (3).

[0041]

[Formula 8]



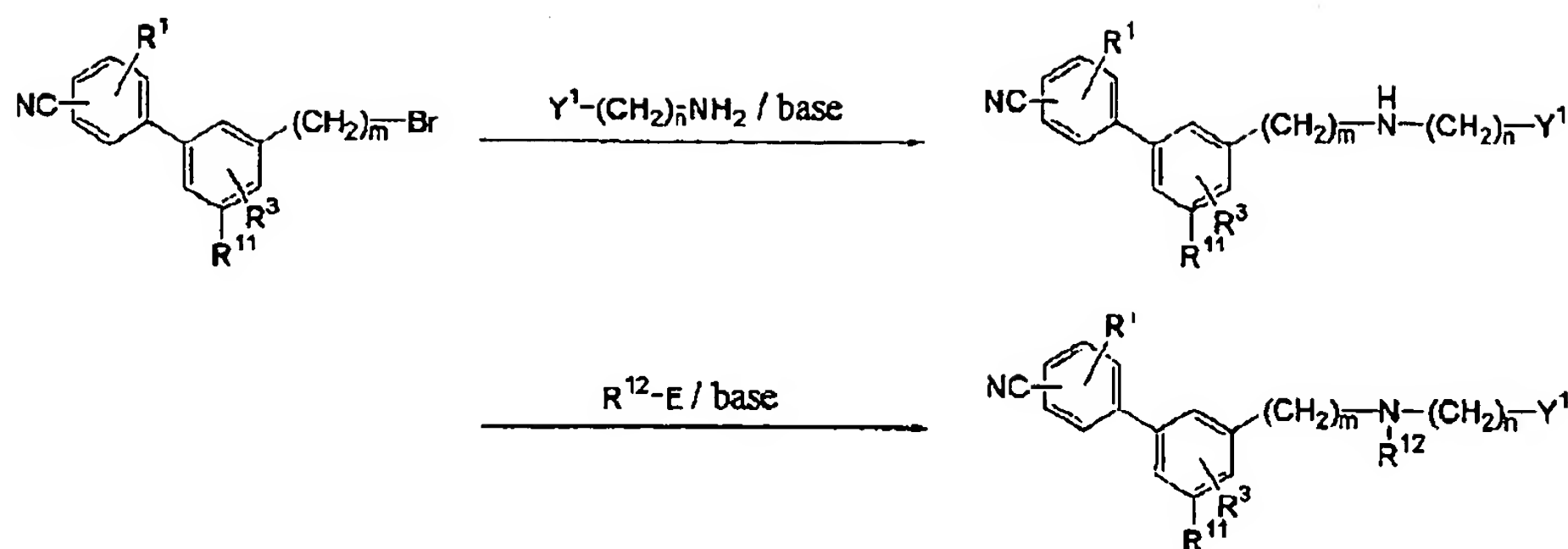
[0042] A³ expresses an amidino group among [formula (3)]. R¹⁰ A carboxyl group, C1 - 4 alkoxy carbonyl group, an aryloxy carbonyl group, an aralkoxy carbonyl machine, a carbamoyl group (the nitrogen atom which constitutes a carbamoyl group) it may be replaced by Monod or G C1 - 4 alkyl groups, or the nitrogen atom of amino acid is sufficient It expresses and X³ expresses the structure shown by formula-NH-, -NH-CO-, -NH-SO₂-, and -NH-CO-NH-. Y³ A phenyl group, a naphthyl group, or 1 - 2 **** aromatic heterocycle machine (these rings) A halogen atom, a hydroxyl group, C1 - 4 alkyl groups, C1 - 4 alkoxy groups, A trifluoromethyl machine, a methylene dioxy machine, C1 - 4 hydroxyalkyl machine, you may have a carboxyl group, C1 - 4 alkoxy carbonyl group, Monod or a G alkylamino machine, 1-pyrrolidino machine, 1-piperidino machine, C1 - 4 amino alkyl group, Monod, or 1-3 G alkylamino alkyl groups Or following formula-NH-CO-Z (the inside of a formula, ZC1 - 10 alkyl groups, or aryl group (the alkyl group or aryl group of the above and Z)) it may be replaced by C1 - 4 alkyl groups, a hydroxyl group, the amino group, Monod or a dialkylamino machine, the halogen atom, C1 - 4 alkoxy groups, the carboxyl group, and C1 - 4 alkoxy carbonyl group it expresses Expressing the basis shown, u is the integer (however, u is not 0 when Y is expressed with formula:-NH-CO-Z.) of 0-1. it expresses] It comes out and they are the biphenyl amidine derivative expressed or its salt permitted pharmacologically.

[0043] The typical synthesis method of this invention compound expressed with a formula (1) below is explained. In this invention, when a raw material compound or a reaction intermediate has substituents, such as a hydroxyl group which may influence a reaction, an amino group, and a carboxyl group, it is desirable that this functional group is protected suitably, and you react the etherification, and make it after an appropriate time desorbed from this protective group. It is the protective group usually used to each substituent as a protective group. If it is the substituent which does not have a bad influence on other portions at the process of protection and a deprotection, there will be especially no limit. as a protective group of a hydroxyl group A trialkylsilyl group, C1 - 4 alkoxy methyl group, a tetrahydropyranyl group, an acyl group, C1 - 4 alkoxy carbonyl group, etc. are mentioned. as a protective group of the amino group C1 - 4 alkoxy carbonyl group, a benzyloxycarbonyl machine, an acyl group, etc. are mentioned, and C1 - 4 alkyl groups, etc. are mentioned as a protective group of a carboxyl group. A deprotection reaction can be performed according to the method usually performed to each protective group.

[0044] The compound with the structure shown by formula:-N(R⁴)- as X¹ among the nitril objects which are precursors of this invention compound expressed with a formula (1) is compoundable with for example, the following reaction formula (a-1) or (a-2) the reaction shown.

[0045]

[Formula 9]

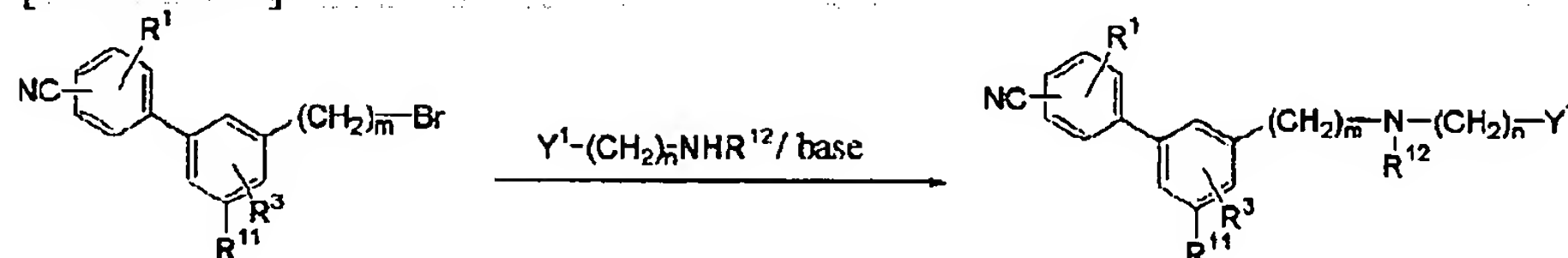


(a - 1)

[0046] R¹, R³, Y¹, m, and n are equal to the definition in a formula (1) among [reaction formula. The fluorine atom among the substituents R₂ as which R¹¹ is defined by the formula (1), a chlorine atom, A bromine atom, a hydroxyl group (or the protector), the amino group (or the protector), C1 - 10 alkoxy groups, and a methoxycarbonyl group are meant, R¹² means the substituent except a hydrogen atom and an aryl group among the substituents R₄ defined by the formula (1), and E means leaving groups, such as chlorine, a bromine, iodine, an acyloxy machine, and a sulfonyloxy machine]

[0047]

[Formula 10]



(a - 2)

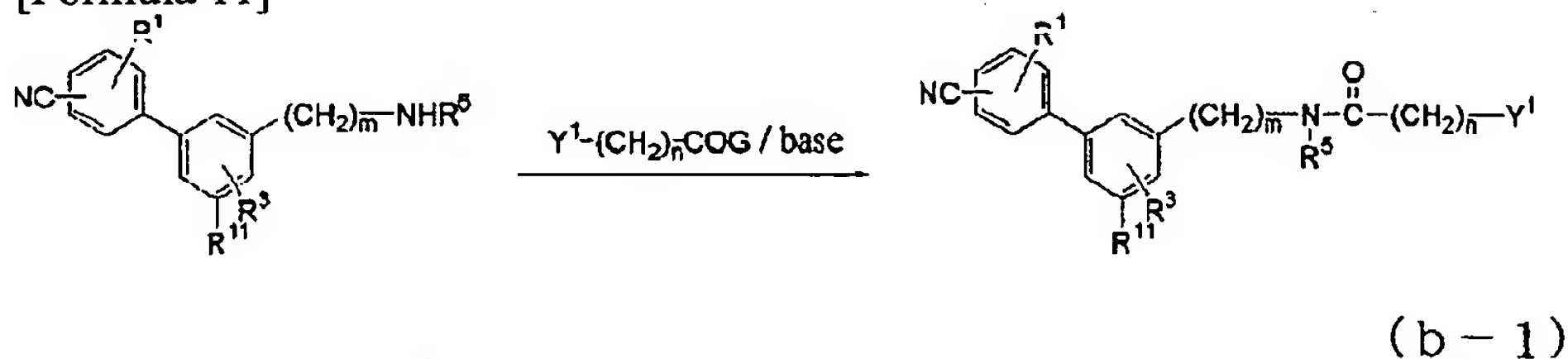
[0048] R¹, R³, Y¹, m, and n are equal to the definition in a formula (1) among [reaction formula. The fluorine atom among the substituents R₂ as which R¹¹ is defined by the formula (1), a chlorine atom, A bromine atom, a hydroxyl group (or the protector), the amino group (or the protector), C1 - 10 alkoxy groups, and a methoxycarbonyl group are meant, R¹² means an aryl group among the substituents R₄ defined by the formula (1), and E means leaving groups, such as chlorine, a bromine, iodine, an acyloxy machine, and a sulfonyloxy machine]

[0049] A reaction formula (a-1) and N-alkylation reaction shown by (a-2) can be performed using a well-known alkylation reaction condition. Namely, by making the amines expressed with Y¹-(CH₂)_n-NH₂ under amines existence, such as mineral salt, such as potassium carbonate which acts as a base, and tertiary amine, react to the biphenyl alkyl bromide of a raw material [whether the alkylating agent which can manufacture the secondary amine object which is this invention compound, and is expressed with R¹²-E to a secondary amine object is made to react, and] The tertiary amine object which is this invention compound can be manufactured by making the amines expressed with Y¹-(CH₂)_n-NHR¹² react to the biphenyl alkyl bromide of a raw material. A reaction usually mixes an alkylating agent and an amine by arbitrary ratios among a suitable solvent, and is performed by stirring for 1 to 96 hours under cooling, a room temperature, or heating. The solvents which do not influence reactions, such as hydrocarbons, such as alcohols, such as a methanol and ethanol, benzene, and toluene, or THF, a dioxane, an acetonitrile, and DMF, DMSO, as a solvent, or those mixed solvents use, using organic tertiary amine, such as mineral salt, such as potassium carbonate and a sodium carbonate, and a triethylamine, a pyridine, as a base, and it is carried out by setting the ratio of an alkylating agent and an amine object to 1:10-10:1. The ratio of an alkylating agent and an amine object is preferably set to 1:5-1:1, and it is carried out under a room temperature or heating for 2 to 24 hours.

[0050] Moreover, the compound which has amide combination as X1 among the nitril objects which are precursors of this invention compound expressed with a formula (1) is compoundable with for example, the following reaction formula (b-1) or (b-2) the reaction shown.

[0051]

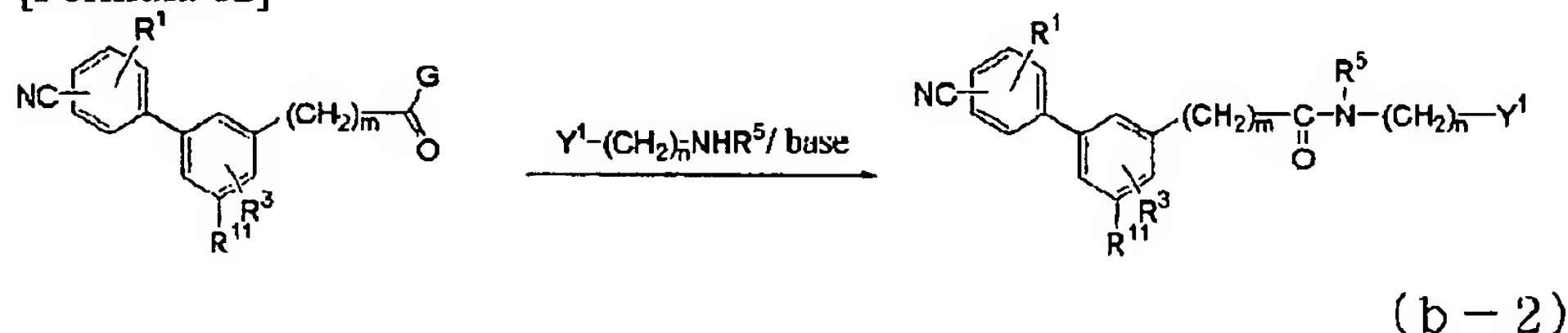
[Formula 11]



[0052] R1, R3, R5, Y1, m, and n are equal to the definition in a formula (1) among [reaction formula. The fluorine atom among the substituents R2 as which R11 is defined by the formula (1), a chlorine atom, meaning a bromine atom, a hydroxyl group (or the protector), the amino group (or the protector), C1 - 10 alkoxy groups, and a methoxycarbonyl group, G means bases, such as a halogen, an acyloxy machine, p-nitroglycerine phenoxy machine, and a hydroxyl group]

[0053]

[Formula 12]



[0054] R1, R3, R5, Y1, m, and n are equal to the definition in a formula (1) among [reaction formula. The fluorine atom among the substituents R2 as which R11 is defined by the formula (1), a chlorine atom, meaning a bromine atom, a hydroxyl group (or the protector), the amino group (or the protector), C1 - 10 alkoxy groups, and a methoxycarbonyl group, G means bases, such as a halogen, an acyloxy machine, p-nitroglycerine phenoxy machine, and a hydroxyl group]

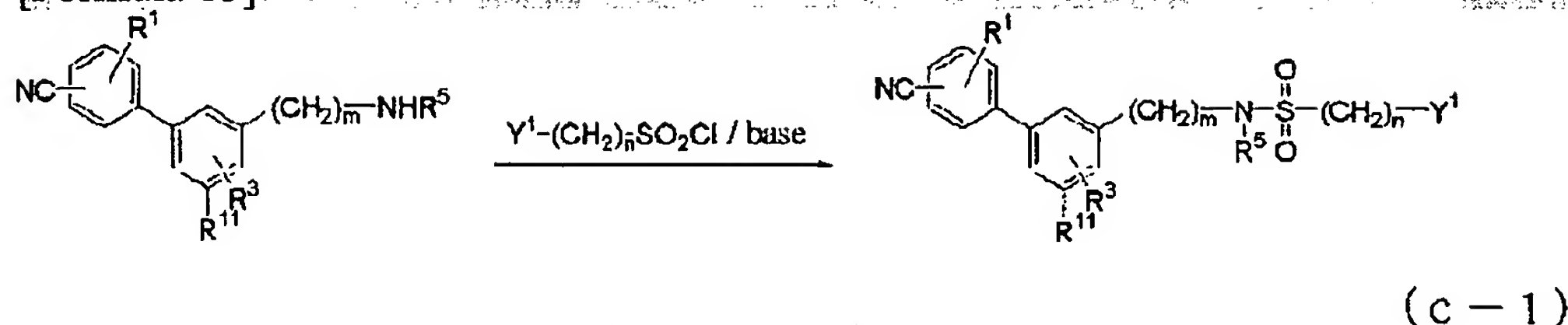
[0055] the above-mentioned reaction formula (b-1) -- or (b-2) can perform a reaction by using the conditions of a well-known amidation reaction. Usually, the activity derivative and amine compound of a carboxylic acid can be mixed among a suitable solvent under existence of a base, and an amide object can be acquired by performing the acylation. As the activity derivative of a carboxylic acid to be used Activity ester, such as acid halide, a mixed acid anhydride, and p-nitrophenol, is used, and it is carried out to the bottom of cooling or a room temperature for 30 minutes to 24 hours. It is preferably carried out at 0-20 degrees C for 1 to 18 hours among solvents, such as aliphatic ether, such as halogenated hydrocarbons, such as a dichloromethane, and THF, diethylether, an acetonitrile, and DMF, or those mixed solvents, using tertiary amine, such as a triethylamine, as a base.

[0056] Moreover, such an amide object can be acquired also by the condensation reaction of amines and a carboxylic acid under condensing-agent existence, such as carbodiimides. In this case, as a solvent, halogenated hydrocarbons, such as DMF and chloroform, are suitable, and N and N-dicyclohexylcarbodiimide, a 1-ethyl-(3-(N and N-dimethylamino) propyl) carbodiimide, carbonyldiimidazole and a diphenyl phosphoryl azide, and a diethyl phosphoryl cyanide are suitable as a condensing agent. A reaction is usually performed under cooling or a room temperature for 2 to 48 hours.

[0057] Moreover, the compound which has sulfonamide structure as X1 among the nitril objects which are precursors of this invention compound expressed with a formula (1) is compoundable with for example, the following reaction formula (c-1) or (c-2) the reaction shown.

[0058]

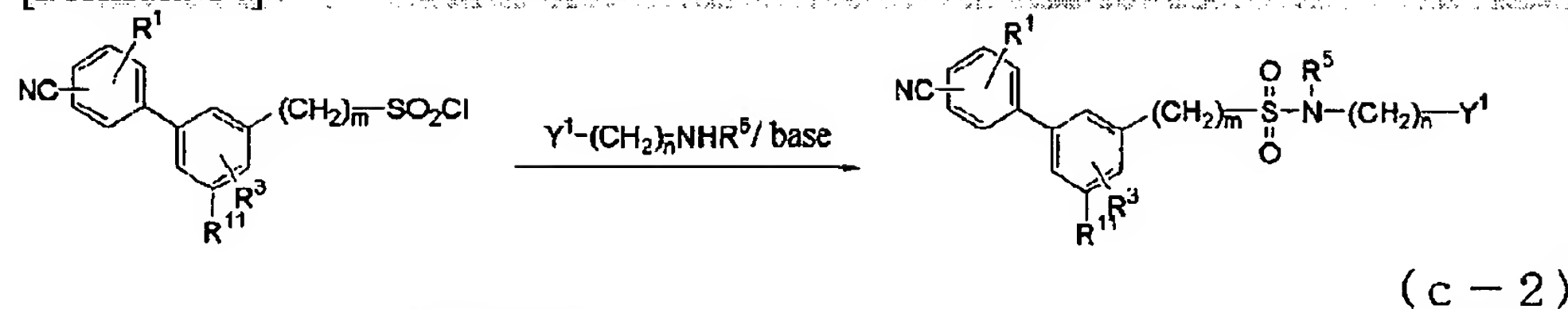
[Formula 13]



[0059] [reaction-formula Naka, and R1, R3, R5, Y1, m and n are equal to the definition in a formula (1), and R11 means a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group (or the protector), the amino group (or the protector), C1 - 10 alkoxy groups, and a methoxycarbonyl group among the substituents R2 defined by the formula (1).]

[0060]

[Formula 14]



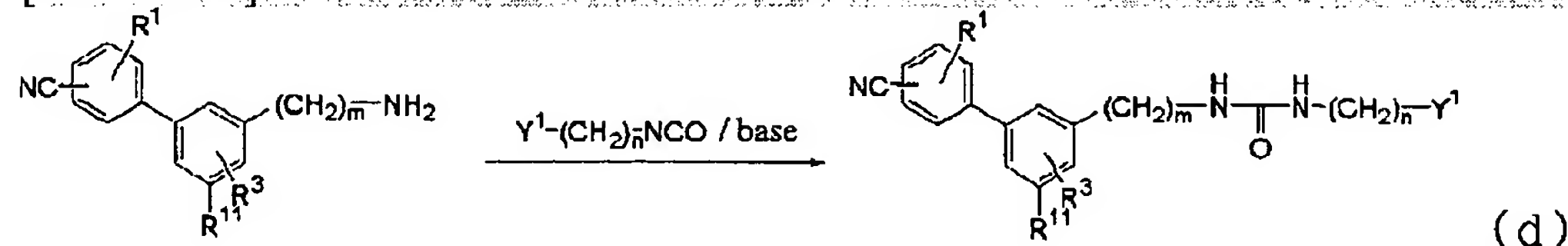
[0061] [reaction-formula Naka, and R1, R3, R5, Y1, m and n are equal to the definition in a formula (1), and R11 means a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group (or the protector), the amino group (or the protector), C1 - 10 alkoxy groups, and a methoxycarbonyl group among the substituents R2 defined by the formula (1).]

[0062] A reaction reaction formula (c-1) or (c-2) the reaction expressed is performed by making the activity derivative of an amine and a sulfonic acid react the bottom of existence of a base, and among a suitable solvent, and the target sulfonamide object can be acquired. As an activity derivative of a sulfonic acid, sulfonyl halide is suitable and is performed at 0-20 degrees C for 1 to 24 hours among solvents, such as aliphatic ether, such as halogenated hydrocarbons, such as a dichloromethane, and THF, diethylether, an acetonitrile, and DMF, or those mixed solvents, using tertiary amine, such as a triethylamine, as a base.

[0063] Moreover, the compound which has urea structure as X1 among the nitril objects which are precursors of this invention compound expressed with a formula (1) is compoundable with the reaction shown for example, by the following reaction formula (d).

[0064]

[Formula 15]



[0065] [reaction-formula Naka, and R1, R3, Y1, m and n are equal to the definition in a formula (1), and R11 means a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group (or the protector), the amino group (or the protector), C1 - 10 alkoxy groups, and a methoxycarbonyl group among the substituents R2 defined by the formula (1).]

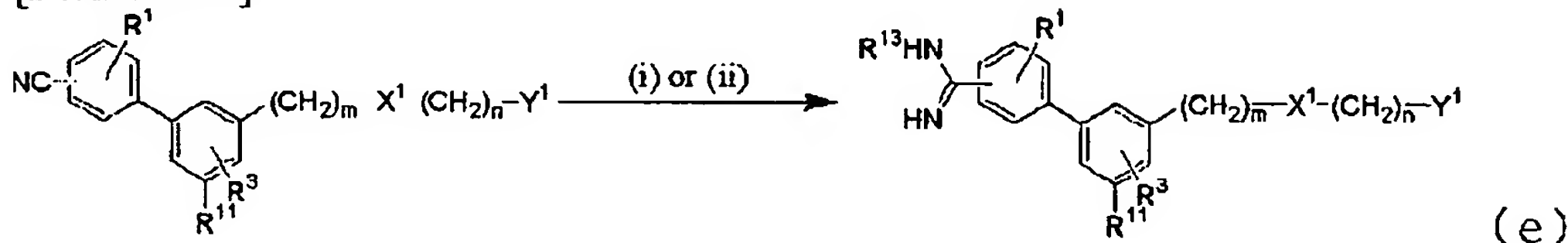
[0066] That is, the compound which has urea structure as X1 can be manufactured by making the amine and isocyanate derivative of a raw material react under suitable cooling among a solvent, or heating. The solvents used at this reaction are DMF, THF, a dioxane, a dichloroethane, chloroform, an acetonitrile,

DMSO, benzene, toluene, etc.

[0067] As mentioned above, the nitril object which is manufactured by the reaction shown by the above-mentioned reaction formula (a-1), (a-2), (b-1), (b-2), (c-1), (c-2), and (d) and which is a precursor of this invention compound is the following reaction formula (e).

[0068]

[Formula 16]



[0069] R1, R3, X1, Y1, m, and n are equal to the definition in a formula (1) among [reaction formula. The fluorine atom among the substituents R2 as which R11 is defined by the formula (1), a chlorine atom, meaning a bromine atom, a hydroxyl group (or the protector), the amino group (or the protector), C1 - 10 alkoxy groups, and a methoxycarbonyl group, R13 means a hydrogen atom, a hydroxyl group, the amino group, C1 - 10 alkyl groups, an aryl group, and an aralkyl machine] By being alike and giving an amidino-ized reaction as shown, it is convertible for the bends amidine derivative which is this invention compound. This amidino-ized reaction is performed by the reaction condition as shown in the following (i) or (ii).

[0070] (i) -- amidino-ized reaction: which passes through IMIDATO-ization using the alcoholic solution of a hydrogen halide -- the reaction which obtains IMIDATO from a nitril object and alcohols advances by dissolving in the alcohols of the carbon numbers 1-4 containing hydrogen halides, such as a hydrogen chloride and a hydrogen bromide, and agitating an alkoxy methylphenyl benzonitrile object A reaction is usually performed at -20-30 degrees C for 12 to 96 hours. It is preferably carried out at -10-+30 degrees C among the methanol of a hydrogen chloride, or an ethanol solution for 24 to 72 hours. The reaction of IMIDATO and ammonia advances by agitating IMIDATO in halogenated hydrocarbons, such as aliphatic ether, such as alcohols of the carbon numbers 1-4, such as a methanol containing ammonia, and ethanol, or diethylether, or a dichloromethane, and chloroform, or those mixed solvents, and the bends amidine derivative (1) which is this invention compound generates it. A reaction is usually performed at the temperature of -10-+50 degrees C for 1 to 48 hours. It is preferably carried out at 0-30 degrees C among a methanol or ethanol for 2 to 12 hours.

[0071] (ii) -- amidino-ized reaction: which passes through IMIDATO which adjusted the hydrogen halide with the entrainment directly -- the reaction of a nitril object and alcohol A nitril object For example, aliphatic ether, such as diethylether, Or, dissolving in aprotic solvents, such as halogenated hydrocarbons, such as chloroform, or benzene, and adding and agitating the alcohols of the equivalent or the superfluous carbon numbers 1-4 - Blow the hydrogen halide of a hydrogen chloride or a hydrogen bromide at 30-0 degree C for 30 minutes to 6 hours, stop an entrainment after that, and go on by agitating at 0-50 degrees C for 3 to 96 hours. Agitating among the halogenated hydrocarbons containing the equivalent, a superfluous methanol, or ethanol preferably, in -10-0 degree C, a hydrogen chloride is blown for 1 to 3 hours, an entrainment is stopped after that, and it agitates at 10-40 degrees C for 8 to 24 hours. Thus, obtained IMIDATO is convertible for the bends amidine derivative (1) which is this invention compound by agitating in halogenated-hydrocarbon solvents, such as aliphatic ether solvents, such as an alcoholic solvent of the carbon numbers 1-4, such as a methanol containing ammonia, and ethanol, or diethylether, or chloroform, or those mixed solvents. A reaction is usually performed at the temperature of -20-+50 degrees C for 1 to 48 hours. It is preferably carried out at 0-30 degrees C among saturated-ammonia ethanol for 2 to 12 hours.

[0072] Moreover, it is manufactured by the ester hydrolysis of the compound which has a methoxycarbonyl group as R9 among the bends amidine compounds manufactured by the above-mentioned reaction formula (e) about the compound which has a carboxyl group as R2 among the compounds shown by the formula (1). This adding-water decomposition reaction can be performed to

the bottom of a basic condition, an acid condition, or neutrality condition if needed. At the reaction under basic conditions, a sodium hydroxide, a potassium hydroxide, a lithium hydroxide, a barium hydroxide, etc. are mentioned as a base to be used, Lewis acids, such as a hydrochloric acid, a sulfuric acid, and boron trichloride, a trifluoroacetic acid, p-toluenesulfonic acid, etc. are mentioned under acid conditions, and enzymes, such as halogen ion, such as an iodation lithium and a lithium bromide, a thiol or an alkali-metal salt of SERENORU, an iodine trimethyl silane, or esterase, are mentioned under neutrality condition. As a solvent used for a reaction, polar solvents, such as water, alcohol, an acetone, a dioxane, and THF, DMF, DMSO, or those mixed solvents are used. a reaction -- usually -- a room temperature or warming -- it carries out in the bottom for 2 to 96 hours Suitable conditions, such as reaction temperature and reaction time, change with reaction conditions to be used, are suitably chosen by the conventional method, and are performed.

[0073] Thus, about the obtained compound which has a carboxyl group as a substituent R2, a carboxyl group is convertible for other ester objects by the method shown in following (iii), (iv), and (v).

[0074] Conversion to the alkoxy carbonyl group of a carboxyl group : The compound which has a carboxyl group as a substituent R2 among the compounds expressed with a formula (4), (iii) the equivalent or a superfluous alkylating agent (for example, an acetoxy methyl chloride --) Acyloxy methyl chlorides or allyl chlorides, such as a PIBARO yloxy methyl chloride, Benzyl chlorides Or the inside of non-proton nature polar solvents, such as aliphatic ether, such as halogenated hydrocarbons, such as a dichloromethane, or THF, or DMF, or those mixed solvents, In -10-+80 degrees C, a carboxyl group is convertible for an alkoxy carbonyl group by making it react for 1 to 48 hours under tertiary amine existence, such as a triethylamine and a diisopropyl ethylamine. Preferably, it is carried out at 20-60 degrees C under diisopropyl ethylamine existence for 2 to 24 hours using an alkylating agent with superfluous equivalent - smallness.

[0075] (iv) -- conversion [to the aralkoxy carbonyl machine of a carboxyl group]: -- if the compound which has a carboxyl group as a substituent R2 among the compounds expressed with a formula (4), and alcohols, such as the equivalent or superfluous benzyl alcohol, are made to react under acid-catalyst existence, such as a hydrogen chloride, a sulfuric acid, and a sulfonic acid, by using halogenated hydrocarbons, such as a dichloromethane, as a solvent, a carboxyl group is convertible for an aralkoxy carbonyl machine A reaction is usually performed under a room temperature or heating for 1 to 72 hours. Preferably, it is carried out at 20-60 degrees C under diisopropyl ethylamine existence for 2 to 24 hours using alcohols with superfluous equivalent - smallness.

[0076] (v) -- conversion [to the aryloxy carbonyl group of a carboxyl group]: -- if the compound which has a carboxyl group as a substituent R2 among the compounds expressed with a formula (4), and the aromatic compound which has hydroxyl groups, such as the equivalent or a superfluous phenol, are made to react under condensing-agent existence, such as a dicyclohexylcarbodiimide, by using aliphatic ether, such as diethylether, as a solvent, a carboxyl group is convertible for an aryloxy carbonyl group A reaction is usually performed at degree C 0 to 50 degrees for 1 to 48 hours. Preferably, it is carried out at a room temperature for 3 to 24 hours.

[0077] Moreover, the compound which has a carboxyl group as R2 makes acid halide the well-known technique, for example, a carboxyl group, by oxalyl chloride etc., is making aqueous ammonia react and can also change it into a carbamoyl group. By making it react with acid halide and an N-methyl-N-methoxy amine similarly, it is convertible for an N-methyl-N-methoxy carbamoyl group, and this reacts with further various alkyl magnesium reaction agents, and can be changed into an alkyl carbonyl group.

[0078] In addition, in addition to this, well-known etherification, amidino-izing, hydrolysis, the formation of alkyl imidoyl, amidation, the esterification, etc. can manufacture the compound shown by the formula (1) by combining arbitrarily the process which this contractor can usually adopt.

[0079] The well-known method, for example, extraction, precipitation, a fractionation chromatography, fractional-crystallization-izing, recrystallization, etc. can isolate and refine the alkoxy methylphenyl bends amidine derivative I manufactured as mentioned above. Moreover, the salt of this invention compound permitted pharmacologically can be manufactured by giving the usual salt formation reaction.

[0080] There is an effect which suppresses FXa activity and the biphenyl amidine derivative of this invention or its salt permitted pharmacologically can be used as a FXa inhibitor as the preventive in which clinical application is possible, and/or a treatment agent to thrombus plug nature disorders, such as myocardial infarction, cerebral thrombosis, deletion artery thrombosis, and deep venous thrombosis.

[0081] Moreover, the biphenyl amidine derivative of this invention can be used as the physic constituent which consists of support permitted pharmaceutically, can cast this physic constituent to various pharmaceutical forms, and can prescribe it for the patient by taking orally or the parenteral. As parenteral administration, medication into a vein, hypodermically, muscles, transderma, the rectum, pernasality, and instillation is mentioned, for example.

[0082] The following is mentioned as a pharmaceutical form of this physic constituent. For example, in the case of an internal use agent, pharmaceutical forms, such as a tablet, the pilule, a granule, powder, solution, suspension, syrup, and a capsule, are mentioned.

[0083] Here, as the molding method of a tablet, it can cast by the usual method using support permitted pharmaceutically, such as an excipient, a binder, and disintegrator. The pilule, a granule, and powder as well as the case of a tablet can be cast by the usual method using an excipient etc. The molding method of solution, the suspension, and the syrup can be cast by the usual method using glycerol esters, alcohols, water, vegetable oil, etc. The molding method of a capsule can cast a granule, powder, or solution by filling up capsules, such as gelatin.

[0084] In the case of a vein, hypodermically, and intramuscular administration, a medicine can be prescribed for the patient as injection among parenteral administration agents. The case where a biphenyl amidine derivative is dissolved in the un-water-soluble solution which consists of organic ester, such as a propylene glycol, a polyethylene glycol, and vegetable oil, as injection when dissolving in water-soluble solution, such as a physiological saline, etc. is mentioned.

[0085] In the case of dermal administration, it can use as pharmaceutical forms, such as an ointment and cream pharmaceuticals. An ointment is mixed with fats and oils, vaseline, etc., a biphenyl amidine derivative is used for it, it can mix with an emulsifier and cream pharmaceuticals can cast a biphenyl amidine derivative.

[0086] In rectum medication, it can consider as a suppository using a gelatin soft capsule etc.

[0087] In pernasal medication, it can use as a tablet which consists of a liquefied or powdered constituent. As a basis of a liquefied agent, water, brine, a phosphate buffer solution, the acetic-acid buffer solution, etc. are used, and a surfactant, the antioxidant, the stabilizer, the preservative, and the viscous grant agent may be included further. As a basis of a powdered agent, for example, damage-at-sea solubility things, such as for example, the thing of water absorptivity, such as polyacrylates of water-solubility, cellulose low-grade alkyl ether, a polyethylene-glycol polyvinyl pyrrolidone, an amylose, and a pullulan, or celluloses, starch, proteins, gums, and bridge formation vinyl polymerization objects, are mentioned, and the thing of water absorptivity is desirable. Moreover, you may mix and use these. Furthermore to a powdered agent, you may add an antioxidant, a coloring agent, a preservative, antiseptics, a **** agent, etc. This liquefied agent and a powdered agent can be prescribed for the patient for example, using a spray instrument etc.

[0088] In the medication in instillation, it can be used as water or non-water ophthalmic solution. A sterilized pure water, a physiological saline, etc. can be used for a solvent as aquosity ophthalmic solution. When only a sterilized pure water is used as a solvent, suspension, such as a surfactant and a macromolecule thickener, can be added and it can use as aquosity suspension eye lotions, and solubilizing agents, such as a nonionic surfactant, can be added and it can also use as solubilization eye lotions. As non-aquosity ophthalmic solution, the non-aquosity solvent for injection can be used for a solvent, and it can use as non-aquosity suspension eye lotions.

[0089] When medicating an eye by methods other than the ophthalmic solution, it can consider [*****] as pharmaceutical forms, such as ophthalmic ointment, application solution, epipastic, and an insertion agent.

[0090] Moreover, when inhaling from a nose, a mouth, etc., it is inhaled, using for example, the aerosol spray for inhalation etc. as the solution or suspension of a biphenyl amidine derivative and the medicine

manufacture excipient generally used. moreover, dryness -- the biphenyl amidine derivative made powdered can be prescribed for the patient using the inhalator contacted lungs and directly [0091] In a tablet various [these], pharmaceutical support permitted, such as an isotonicizing agent, a preservative, antiseptics, a wetting agent, a buffer, an emulsifier, a dispersant, and a stabilizer, can be added if needed.

[0092] Moreover, if needed, it can deal with combination of a germicide, the filtration using the bacterium hold filter, heating, irradiation, etc. for a tablet various [these], and can be made sterile to it. Or a sterile solid tablet is manufactured, and it can also be used for a sterile solution suitable just before use, dissolving or suspending.

TECHNICAL FIELD JP2000-178243

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2. **** shows the word which can not be translated.
3. In the drawings, any words are not translated.

TECHNICAL FIELD

[The technical field to which invention belongs] this invention relates to the new alternative Xth factor (it omits Following FXa) inhibitor of activation blood coagulation shown by the formula (1).
[0002]

[Translation done.]

PRIOR ART JP 2000-178243

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PRIOR ART

[Description of the Prior Art] Anticoagulant therapy is bearing the role important as medical treatment and a prophylaxis to thrombus plug nature disorders, such as myocardial infarction, cerebral thrombosis, peripheral artery thrombosis, and deep venous thrombosis.

[0003] In prevention of chronic thrombosis, the safe and suitable oral anticoagulant in which prolonged administration is possible is especially required. However, in the present condition, a walfarin potassium with difficult control of anticoagulation ability only exists, and the anticoagulant which is easier to use is called for.

[0004] It was known that there is a danger that an antithrombin agent will cause a bleeding inclination as a side effect which is looked at by the hirudine, for example although development is furthered as an anticoagulant from the former. It is becoming clear that suppression of FXa located in the upstream of a thrombin in a blood coagulation cascade is more efficient than suppression of a thrombin in mechanism, and such a side effect is weak in a FXa inhibitor, and it is clinically desirable.

[0005] the biphenyl amidine compound in which FXa prevention activity is shown -- the 17th May Day SHINARU chemistry symposium, the collection of the 6th physic chemistry sectional meeting annual convention summaries, and 184- it is indicated by 185 and 1997 However, this invention compound is a new compound which is clearly different on structure in that the hetero atom is utilized for combination with the cyclic structure which will interact with the biphenyl amidine structure which will interact with S1 pocket, and the aryl joint site.

[0006] Moreover, although the annular imino derivative (JP,4-264068,A) is indicating the biphenyl amidine derivative, this inventions differ clearly at the point which is carrying out combination by the hetero atom with the benzylic position.

[Translation done.]

EFFECT OF THE INVENTION

* NOTICES *

JP2000-178243

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EFFECT OF THE INVENTION

[Effect of the Invention] the biphenyl amidine derivative of this invention or its salt permitted pharmacologically has the effect which suppresses FXa activity, and it twisted that it was clear that it is possible to use it as a FXa inhibitor to thrombus plug nature diseases, such as myocardial infarction, cerebral thrombosis, peripheral artery thrombosis, and depths vein thrombosis, as the preventive in which clinical application is possible, and/or a medical treatment agent.

[Translation done.]

TECHNICAL PROBLEM

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TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] The purpose of this invention is offering the new compound which may serve as a FXa inhibitor in which clinical application is possible.

[Translation done.]

MEANS JP2000-178243

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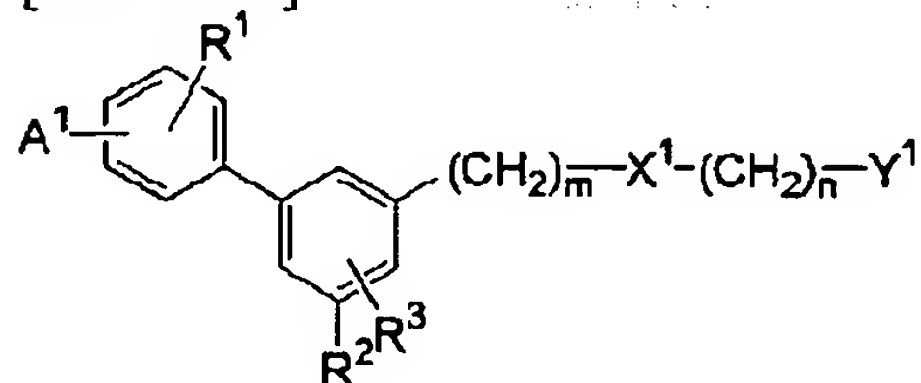
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MEANS

[Means for Solving the Problem] This invention persons are the following formulas (1), as a result of repeating examination wholeheartedly, in order to attain the above-mentioned purpose.

[0009]

[Formula 6]

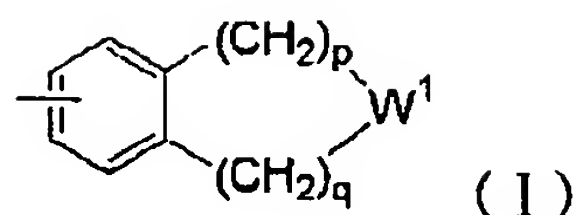


(1)

[0010] A1 expresses an amidino group among [formula (1)]. R1 A hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, the amino group, a nitro group, C1 - 10 alkyl groups, C1 - 10 alkoxy groups are expressed. or R2 A fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, the amino group, C1 - 10 alkoxy groups, A carboxyl group, C1 - 10 alkoxy carbonyl group, an aryloxy carbonyl group, an aralkoxy carbonyl machine, a carbamoyl group (the nitrogen atom which constitutes a carbamoyl group) it may be replaced by Monod, or G C1 - 10 alkyl groups, or the nitrogen atom of amino acid is sufficient C1 - 10 alkyl carbonyl group, C1 - 10 alkyl sulfenyl machine, C1 - 10 alkyl sulfinyl machine, C1 - 10 alkyl sulfonyl machine, Monod or G C1 - 10 alkylamino machine, Monod, or G C1 - 10 alkylamino sulfonyl machine, A sulfonic group, a phosphono machine, a screw (hydroxy carbonyl) methyl group, a screw (alkoxy carbonyl) methyl group, or 5-tetrazolyl group is expressed. R3 A hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, the amino group, a nitro group, C1 - 10 alkyl groups, C1 - 10 alkoxy groups, a carboxyl group, or C1 - 10 alkoxy carbonyl group is expressed. X1 Formula-NH-CO-NH-, -N(R4)-, -CO-N(R5)-, -N(R5)-CO-, -N(R5)-SO2-, -SO2-N (R5) - (R4 among a formula) expressing a hydrogen atom, C1 - 10 alkyl groups, C1 - 10 alkyl carbonyl group, and C1 - 10 alkyl sulfonyl machine, R5 expresses a hydrogen atom, C1 - 10 alkyl groups, and an aryl group Expressing, Y1 is a phenyl group, a naphthyl group, or 1 - 2 **** aromatic heterocycle machine (these rings). A halogen atom, a hydroxyl group, C1 - 10 alkyl groups, C1 - 10 alkoxy groups, A trifluoromethyl machine, an aryl group, a methylene dioxy machine, C1 - 10 hydroxyalkyl machine, A carboxyl group, C1 - 4 alkoxy carbonyl group, C1 - 10 alkyl sulfenyl machine, C1 - 10 alkyl sulfinyl machine, C1 - 10 alkyl sulfonyl machine, you may have 1-3 substituents, such as Monod or a G alkylamino machine, 1-pyrrolidino machine, 1-piperidino machine, C1 - 10 amino alkyl group, Monod or a G alkylamino alkyl group, a sulfonic group, and a phosphono machine Or the following formula (I)

[0011]

[Formula 7]



[0012] (The inside of a formula (I) and W1 are combination or formula-O-, -O-CO-, and -N(R6)- (R6 among a formula).) a hydrogen atom, C1 - 10 alkyl groups, C1 - 10 alkyl carbonyl group, C1 - 10 alkyl sulfonyl machine, or an aryl group is expressed expressing the structure shown, p and q express the integer of 0-3 which fill $4 \geq p+q \geq 2$ ($4 \geq p+q \geq$ when [however,] W1 shows combination 3) The basis shown or following formula-NH-CO-Z (the inside of a formula, ZC1 - 10 alkyl groups, or aryl group (the alkyl group or aryl group of the above and Z)) it may be replaced by C1 - 4 alkyl groups, a hydroxyl group, the amino group, Monod or a dialkylamino machine, the halogen atom, C1 - 4 alkoxy groups, the carboxyl group, and C1 - 4 alkoxy carbonyl group it expresses The basis shown is expressed, m expresses the integer of 1-3, and n is the integer (however, n is not 0 when Y1 is expressed with formula:-NH-CO-Z1.) of 0-3. it expresses] Come out, the biphenyl amidine derivative expressed or its salt permitted pharmacologically is found out, and it comes to complete this invention.

[0013] Hereafter, this invention is explained in detail. In the above-mentioned definition to the substituent of the compound of the formula in this specification (1), a formula (2), or a formula (3) with "C1 - 4 alkyl groups" The shape of a straight chain which has 1-4 carbon numbers, the letter of branching, or an annular hydrocarbon group is meant. For example, a methyl group, an ethyl group, a propyl group, an isopropyl machine, a butyl, an isobutyl machine, a tert-butyl, a cyclo propyl group, etc. are expressed, and a methyl group, an ethyl group, a propyl group, and an isopropyl machine are desirable especially.

[0014] The shape of a straight chain which has 1-10 carbon numbers with "C1 - 10 alkyl groups", The letter of branching or an annular hydrocarbon group is meant. For example, a methyl group, an ethyl group, A propyl group, an isopropyl machine, a butyl, an isobutyl machine, a tert-butyl, A pentyl machine, a neopentyl machine, an isopentyl machine, 1, 2-dimethyl propyl group, Hexyl machine, iso hexyl machine, 1, and 1-dimethyl butyl, 2, and 2-dimethyl butyl, 1-ethyl butyl, 2-ethyl butyl, a heptyl machine, an iso heptyl machine, 1-methyl hexyl, 2-methyl hexyl, an octyl machine, a 2-ethylhexyl machine, A nonyl machine, a decyl group or 1-methyl nonyl machine, a cyclo propyl group, A cyclo butyl, a cyclopentyl group, a cyclohexyl machine, a cycloheptyl machine, A cyclo octyl machine, an adamantyl machine, etc. are expressed. especially A methyl group, an ethyl group, A propyl group, an isopropyl machine, a butyl, a tert-butyl, and a cyclohexyl machine are desirable, and especially when it is the substituent contained especially in substituents Y1 and Y2 or Y3, a methyl group, an ethyl group, and an isopropyl machine are desirable.

[0015] Specifically, an "aryl group" means ring machines, such as a phenyl group, a naphthyl group, a thiophenyl machine, and a pyridyl machine, and is a phenyl group and a naphthyl group preferably.

[0016] Specifically, a benzyl, a phenethyl machine, a phenylpropyl machine, 1-naphthyl methyl group, 2-naphthyl methyl group, etc. are mentioned, and an "aralkyl machine" is a benzyl preferably.

[0017] The carbonyl group which has ** with the straight chain of 1-4 carbon numbers, the letter of branching, or an annular alkyl side chain as "C1 - a 4 alkyl carbonyl group" is expressed, for example, a formyl machine, an acetyl group, a propionyl machine, a butyryl machine, an isobutyryl machine, a pivaloyl machine, etc. are meant, and they are the acetyl group of 1-3 carbon numbers, and a propionyl machine preferably.

[0018] As "C1 - a 10 alkyl carbonyl group" A carbonyl group with the straight chain, the letter of branching, or the annular chain which has 1-10 carbon numbers is expressed. For example, a formyl machine, an acetyl group, a pro PIONIORU machine, a butyryl machine, an isobutyryl machine, A valeryl machine, an iso valeryl machine, a pivaloyl machine, a hexa noil machine, a HEPUTA noil machine, An octanoyl group, a nonanoyl machine, a cyclopentyl carbonyl group, a cyclohexyl carbonyl group, etc. are meant, and they are the acetyl group of 1-8 carbon numbers, a propionyl machine, a butyryl machine, a hexa noil machine, and an octanoyl group preferably.

[0019] A "aryl carbonyl group" means a benzoyl, 4-methoxy benzoyl, 3-trifluoromethyl benzoyl, or the

carbonyl group that the heterocycle combined, and is a benzoyl preferably.

[0020] An "aryloxy carbonyl group" means a phenoxy carbonyl group, a naphthyloxy carbonyl group, 4-methylphenoxy carbonyl group, 3-chloro phenoxy carbonyl group, 4-methoxy phenoxy carbonyl group, or an indan-5-yloxy carbonyl group, and is a phenoxy carbonyl group and an indan-5-yloxy carbonyl group preferably.

[0021] An "aralkoxy carbonyl machine" means a benzyloxycarbonyl machine, 4-methoxybenzyloxy carbonyl group, 3-trifluoromethyl benzyloxycarbonyl machine, a 3-OKISOHIDOROISO benzofuranyl oxy-carbonyl group, etc., and is a benzyloxycarbonyl machine and a 3-OKISOHIDOROISO benzofuranyl oxy-carbonyl group preferably.

[0022] With "C1 - 4 alkoxy carbonyl group", a methoxycarbonyl group, An ethoxycarbonyl machine, a propoxy carbonyl group, an isopropoxy carbonyl group, A butoxycarbonyl machine, an iso butoxycarbonyl machine, and a sec-butoxycarbonyl machine, The carbonyl group replaced by the alkoxyl group of the carbon numbers 1-4, such as a tert-butoxycarbonyl machine and an acetoxymachine, is meant. preferably It is a methoxycarbonyl group and an ethoxycarbonyl machine, and when it is the substituent contained especially in substituents Y1 and Y2 or Y3, a methoxycarbonyl group and an ethoxycarbonyl machine are desirable.

[0023] With "C1 - 10 alkoxy carbonyl group" A methoxycarbonyl group, an ethoxycarbonyl machine, a propoxy carbonyl group, An isopropoxy carbonyl group, a butoxycarbonyl machine, an iso butoxycarbonyl machine, A sec-butoxycarbonyl machine, a tert-butoxycarbonyl machine, A pentyloxy carbonyl group, an isopentyloxy carbonyl group, a neopentyl oxy-carbonyl group, A hexyloxy carbonyl group, a heptyloxy carbonyl group, an octyloxy carbonyl group, Or an acetoxymachine, a pivaloyloxy machine, Or 5-methyl-3-oxo -The methoxycarbonyl group replaced by the alkoxyl group of the carbon numbers 1-10, such as 2 and 4-dioxo RENIRU machine, is meant. preferably A methoxycarbonyl group, an ethoxycarbonyl machine, a propoxy carbonyl group, An isopropoxy carbonyl group, an acetoxymethyloxy carbonyl group, A pivaloyloxymethyloxy carbonyl group, a methyloxy (5-methyl-3-oxo-2, 4-dioxo nil) carbonyl group, When it is an ethoxycarbonyloxy ethyloxy carbonyl group and is the substituent contained especially in substituents Y1 and Y2 or Y3, a methoxycarbonyl group and an ethoxycarbonyl machine are desirable.

[0024] "C1 - 4 alkoxy groups" mean the alkoxy group which has 1-4 carbon numbers, and are specifically a methoxy machine, an ethoxy basis, a propoxy group, an isopropoxy group, a butoxy machine, an iso butoxy machine, a sec-butoxy machine, a tert-butoxy machine, etc., a methoxy machine, an ethoxy basis, and an isopropyl machine are desirable especially, and when it is the substituent contained especially in substituents Y1 and Y2 or Y3, a methoxy machine and an ethoxy basis are

[0025] "C1 - 10 alkoxy groups" mean the alkoxy group which has 1-10 carbon numbers. Specifically A methoxy machine, an ethoxy basis, a propoxy group, an isopropoxy group, A butoxy machine, an iso butoxy machine, a sec-butoxy machine, a tert-butoxy machine, A pentyloxy machine, a neopentyl oxy-basis, and a tert-pentyloxy machine, 2-methyl butoxy machine, a hexyloxy machine, an iso hexyloxy machine, A heptyloxy machine, an iso heptyloxy machine, an octyloxy machine, an iso octyloxy machine, It is a cyclohexyloxy machine etc., the methoxy machine of 1-6 carbon numbers, an ethoxy basis, and a cyclohexyl machine are desirable especially, and when it is the substituent contained especially in substituents Y1 and Y2 or Y3, a methoxy machine and an ethoxy basis are desirable.

[0026] "C1 - 4 alkyl sulfenyl machine" mean the alkyl sulfenyl machine which has 1-4 carbon numbers, specifically express a methylthio machine, an ethyl thio machine, a butyl thio machine, an isobutyl thio machine, etc., and are a methylthio machine preferably.

[0027] "C1 - 10 alkyl sulfenyl machine" mean the alkyl sulfenyl machine which has 1-10 carbon numbers, specifically express a methylthio machine, an ethyl thio machine, a butyl thio machine, an isobutyl thio machine, a pentyl thio machine, a hexyl thio machine, a heptyl thio machine, an octyl thio machine, etc., and are a methylthio machine preferably.

[0028] "C1 - 4 alkyl sulfinyl machine" mean the alkyl sulfinyl machine which has 1-4 carbon numbers, specifically express a methyl sulfinyl machine, an ethyl sulfinyl machine, a butyl sulfinyl machine, etc., and are a methyl sulfinyl machine preferably.

[0029] "C1 - 10 alkyl sulfinyl machine" mean the alkyl sulfinyl machine which has 1-10 carbon numbers, specifically express a methyl sulfinyl machine, an ethyl sulfinyl machine, a butyl sulfinyl machine, a hexyl sulfinyl machine, an octyl sulfinyl machine, etc., and are a methyl sulfinyl machine preferably.

[0030] "C1 - 4 alkyl sulfonyl machine" mean the alkyl sulfonyl machine which has 1-4 carbon numbers, are specifically a methyl sulfonyl machine, an ethyl sulfonyl machine, and a butyl sulfonyl machine, and are a methyl sulfonyl machine preferably.

[0031] "C1 - 10 alkyl sulfonyl machine" mean the alkyl sulfonyl machine which has 1-10 carbon numbers. Specifically A methyl sulfonyl machine, an ethyl sulfonyl machine, a propyl sulfonyl machine, An isopropyl sulfonyl machine, a butyl sulfonyl machine, an isobutyl sulfonyl machine, A pentyl sulfonyl machine, an isopentyl sulfonyl machine, a neopentyl sulfonyl machine, A hexyl sulfonyl machine, a heptyl sulfonyl machine, an octyl sulfonyl machine, A nonyl sulfonyl machine, a desyl sulfonyl machine, a cyclohexyl sulfonyl machine, etc. are expressed, and the methyl sulfonyl machine of 1-8 carbon numbers, an ethyl sulfonyl machine, a butyl sulfonyl machine, a hexyl sulfonyl machine, and especially an octyl sulfonyl machine are desirable especially.

[0032] With "Monod or a G alkylamino machine" A methylamino machine, a dimethylamino machine, an ethylamino machine, a propylamino machine, A diethylamino machine, an isopropylamino machine, a diisopropylamino machine, A dibutylamino machine, a butylamino machine, the isobutyl amino group, and a sec-butylamino machine, A tert-butylamino machine, a pentylamino machine, a hexylamino machine, The heptyl amino group, the octyl amino group, a cyclopentylamino machine, a cyclohexylamino machine, etc. are meant. It is a methylamino machine, a dimethylamino machine, an ethylamino machine, a diethylamino machine, and a propylamino machine preferably, and especially when it is the substituent contained especially in substituents Y1 and Y2 or Y3, a dimethylamino machine and a diethylamino machine are desirable.

[0033] "Monod contained in substituents Y1 and Y2 or Y3 -- or With a G alkylamino alkyl group", specifically A methylamino methyl group, A dimethyl aminomethyl machine, a diethyl aminomethyl machine, a methylamino ethyl group, A dimethylaminoethyl machine, an ethylamino ethyl group, a diethylaminoethyl machine, A methylaminopropyl machine, a dimethylamino propyl group, an ethylaminopropyl machine, A diethylamino propyl group, a methylamino butyl, a dimethylamino butyl, etc. are meant, and they are a dimethyl aminomethyl machine, a diethyl aminomethyl machine, and a diethylaminoethyl machine preferably.

[0034] Substituents Y1 and Y2, or "C1 - 4 amino alkyl group" contained in Y3 expresses the alkyl group of the carbon numbers 1-4 replaced by the amino group, specifically means an aminomethyl machine, 1-aminoethyl machine, 2-aminoethyl machine, 1-aminopropyl machine, 2-aminopropyl machine, 3-aminopropyl machine, etc., and are an aminomethyl machine, 1-aminomethyl machine, 2-aminoethyl machine, and 1-aminopropyl machine preferably.

[0035] With "Monod or a G alkylamino sulfonyl machine" Specifically A methylamino sulfonyl machine, a dimethylamino sulfonyl machine, An ethylamino sulfonyl machine, a propylamino sulfonyl machine, a diethylamino sulfonyl machine, An isopropylamino sulfonyl machine, a diisopropylamino sulfonyl machine, A dibutylamino sulfonyl machine, a butylamino sulfonyl machine, an isobutyl amino sulfonyl machine, A sec-butylamino sulfonyl machine, a tert-butylamino sulfonyl machine, A pentylamino sulfonyl machine, a hexylamino sulfonyl machine, a heptyl amino sulfonyl machine, An octyl amino sulfonyl machine etc. is meant. preferably A methylamino sulfonyl machine, It is a dimethylamino sulfonyl machine, an ethylamino sulfonyl machine, a diethylamino sulfonyl machine, and a propylamino sulfonyl machine, and they are a methylamino sulfonyl machine and a dimethylamino sulfonyl machine still more preferably.

[0036] A screw (methoxycarbonyl) methyl group, a screw (ethoxycarbonyl) methyl group, etc. are specifically expressed as a "screw (alkoxy carbonyl) methyl group", and it is a screw (methoxycarbonyl) methyl group preferably.

[0037] "C1 - 4 hydroxyalkyl machine" express the alkyl group of the carbon numbers 1-4 replaced by the hydroxyl. Specifically A hydroxymethyl group, 1-hydroxyethyl machine, 2-aminoethyl machine, 1-

hydroxypropyl machine, 2-hydroxypropyl machine, 3-hydroxypropyl machine, etc. are meant. preferably It is a hydroxymethyl group, 1-hydroxyethyl machine, 2-hydroxyethyl machine, and 1-hydroxypropyl machine, and a hydroxymethyl group is desirable when it is the substituent contained especially in substituents Y1 and Y2 or Y3.

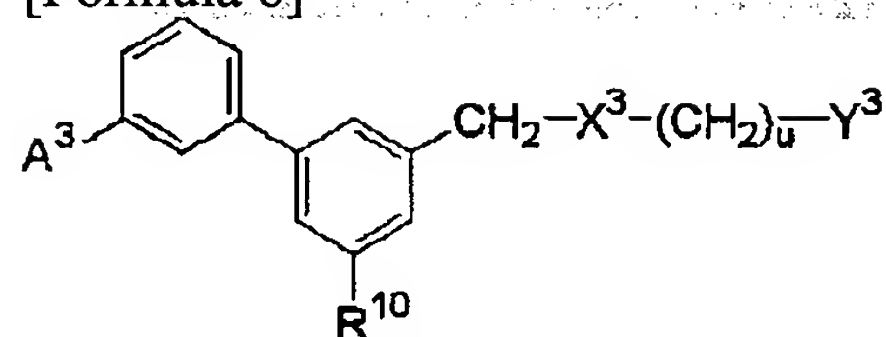
[0038] With substituents Y1 and Y2 or "1 - 2 **** aromatic heterocycle" contained in Y3 1 which has an oxygen atom, a sulfur atom, and/or 1-3 nitrogen atoms as a hetero atom - 2 **** aromatic heterocycle are meant. Specifically A furan ring, a thiophene ring, a pyrrole ring, a pyridine ring, a pyrazine ring, An imidazole ring, a triazole ring, an oxazole ring, an isoxazole ring, A thiazole ring, a thiadiazole ring, the Indore ring, a benzimidazole ring, They are a bends triazole ring, a quinoline ring, an isoquinoline ring, a benzofuran ring, and a bends thiophene ring. as the suitable example A thiophene ring, a thiazole ring, a pyrrole ring, a pyridine ring, the Indore ring, an imidazole ring, a triazole ring, a benzimidazole ring, and a quinoline ring are mentioned.

[0039] this invention compound (1) may form an acid addition salt. Moreover, a salt with a base may be formed depending on the kind of substituent. Although it will not be limited especially if such a salt is a salt permissible in physic Specifically A hydrochloride, the hydrobromate, hydrogen iodide acid chloride, phosphate, a nitrate, Mineral-acid salts, such as a sulfate; Methanesulfon acid chloride, a 2-hydroxy ethane-sulfonic-acid salt, Organic sulfonates [, such as a p-toluenesulfonic-acid salt,]; and acetate, a trifluoroacetic-acid salt, A propionate, an oxalate, chestnut acid chloride, the succinate, a glutarate, Organic carboxylates, such as an adipate, a tartrate, a maleate, a malate, and a mandelic-acid salt, are contained as an acid addition salt. A salt with organic bases, such as a salt with inorganic bases, such as sodium salt, potassium salt, magnesium salt, a calcium salt, and an aluminum salt, and a monomethylamine salt, an ethylamine salt, a lysine salt, an ornithine salt, is mentioned as a salt with a base.

[0040] The desirable range of the compound of this invention is the following formula (3).

[0041]

[Formula 8]



(3)

[0042] A3 expresses an amidino group among [formula (3)]. R10 A carboxyl group, C1 - 4 alkoxy carbonyl group, an aryloxy carbonyl group, an aralkoxy carbonyl machine, a carbamoyl group (the nitrogen atom which constitutes a carbamoyl group) it may be replaced by Monod or G C1 - 4 alkyl groups, or the nitrogen atom of amino acid is sufficient It expresses and X3 expresses the structure shown by formula-NH-, -NH-CO-, -NH-SO2-, and -NH-CO-NH-. Y3 A phenyl group, a naphthyl group, or 1 - 2 **** aromatic heterocycle machine (these rings) A halogen atom, a hydroxyl group, C1 - 4 alkyl groups, C1 - 4 alkoxy groups, A trifluoromethyl machine, a methylene dioxy machine, C1 - 4 hydroxyalkyl machine, you may have a carboxyl group, C1 - 4 alkoxy carbonyl group, Monod or a G alkylamino machine, 1-pyrrolidino machine, 1-piperidino machine, C1 - 4 amino alkyl group, Monod, or 1-3 G alkylamino alkyl groups Or following formula-NH-CO-Z (the inside of a formula, ZC1 - 10 alkyl groups, or aryl group (the alkyl group or aryl group of the above and Z)) it may be replaced by C1 - 4 alkyl groups, a hydroxyl group, the amino group, Monod or a dialkylamino machine, the halogen atom, C1 - 4 alkoxy groups, the carboxyl group, and C1 - 4 alkoxy carbonyl group it expresses Expressing the basis shown, u is the integer (however, u is not 0 when Y is expressed with formula:-NH-CO-Z.) of 0-1. it expresses] It comes out and they are the biphenyl amidine derivative expressed or its salt permitted pharmacologically.

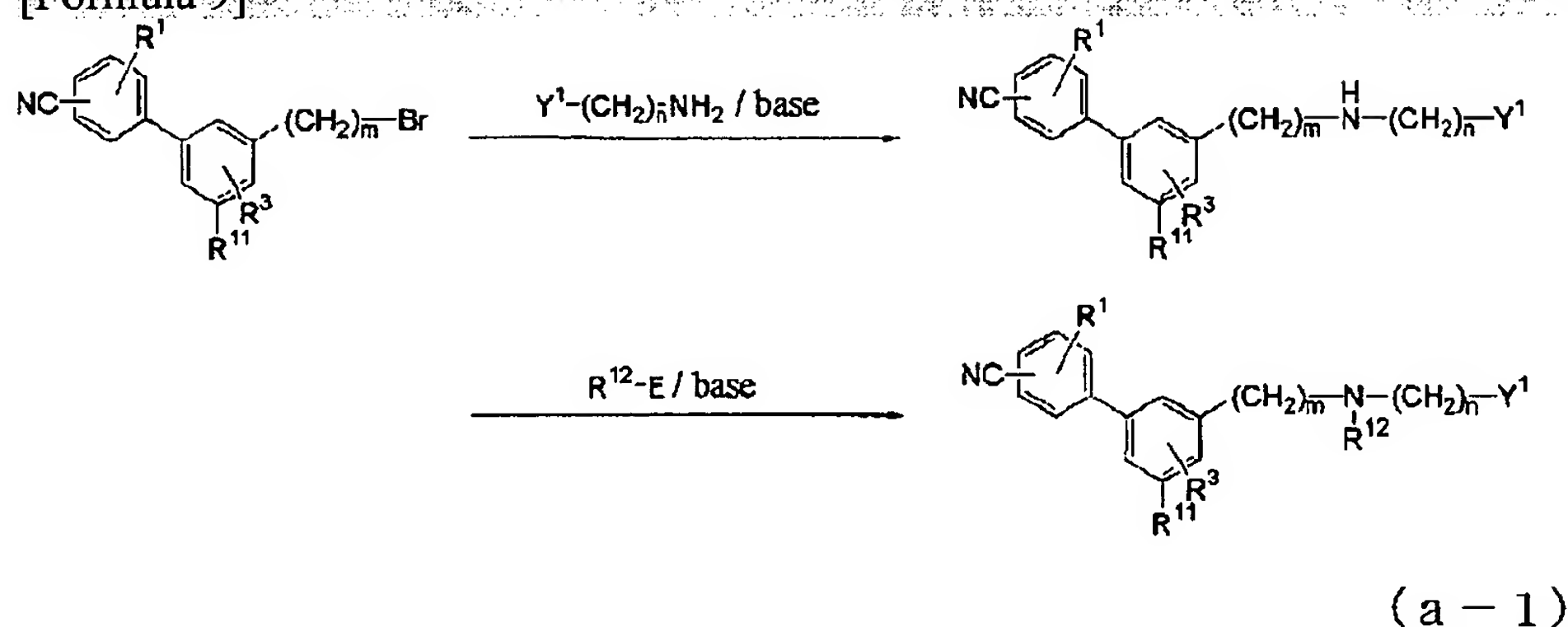
[0043] The typical synthesis method of this invention compound expressed with a formula (1) below is explained. In this invention, when a raw material compound or a reaction intermediate has substituents, such as a hydroxyl group which may influence a reaction, an amino group, and a carboxyl group, it is

desirable that this functional group is protected suitably, and you react the etherification, and make it after an appropriate time desorbed from this protective group. It is the protective group usually used to each substituent as a protective group. If it is the substituent which does not have a bad influence on other portions at the process of protection and a deprotection, there will be especially no limit. as a protective group of a hydroxyl group A trialkylsilyl group, C1 - 4 alkoxy methyl group, a tetrahydropyranyl group, an acyl group, C1 - 4 alkoxy carbonyl group, etc. are mentioned. as a protective group of the amino group C1 - 4 alkoxy carbonyl group, a benzyloxycarbonyl machine, an acyl group, etc. are mentioned, and C1 - 4 alkyl groups, etc. are mentioned as a protective group of a carboxyl group. A deprotection reaction can be performed according to the method usually performed to each protective group.

[0044] The compound with the structure shown by formula: -N(R4)- as X1 among the nitril objects which are precursors of this invention compound expressed with a formula (1) is compoundable with for example, the following reaction formula (a-1) or (a-2) the reaction shown.

[0045]

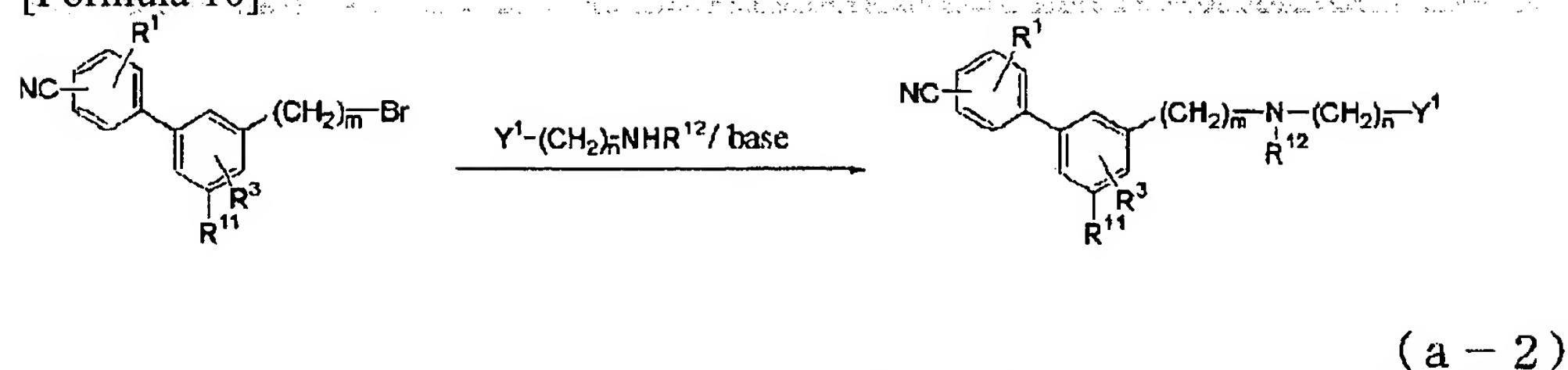
[Formula 9]



[0046] R1, R3, Y1, m, and n are equal to the definition in a formula (1) among [reaction formula. The fluorine atom among the substituents R2 as which R11 is defined by the formula (1), a chlorine atom, A bromine atom, a hydroxyl group (or the protector), the amino group (or the protector), C1 - 10 alkoxy groups, and a methoxycarbonyl group are meant, R12 means the substituent except a hydrogen atom and an aryl group among the substituents R4 defined by the formula (1), and E means leaving groups, such as chlorine, a bromine, iodine, an acyloxy machine, and a sulfonyloxy machine]

[0047]

[Formula 10]



[0048] R1, R3, Y1, m, and n are equal to the definition in a formula (1) among [reaction formula. The fluorine atom among the substituents R2 as which R11 is defined by the formula (1), a chlorine atom, A bromine atom, a hydroxyl group (or the protector), the amino group (or the protector), C1 - 10 alkoxy groups, and a methoxycarbonyl group are meant, R12 means an aryl group among the substituents R4 defined by the formula (1), and E means leaving groups, such as chlorine, a bromine, iodine, an acyloxy machine, and a sulfonyloxy machine]

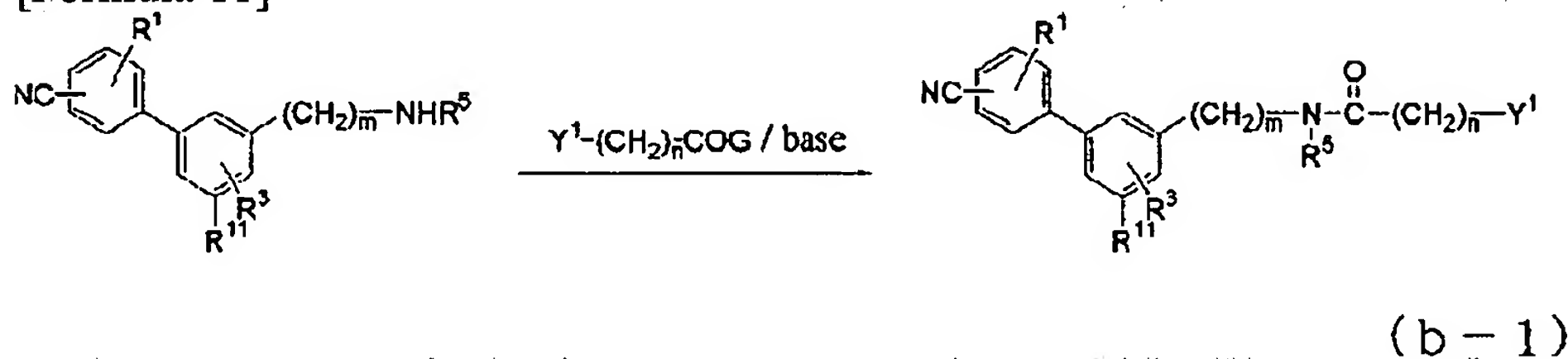
[0049] A reaction formula (a-1) and N-alkylation reaction shown by (a-2) can be performed using a

well-known alkylation reaction condition. Namely, by making the amines expressed with $Y^1-(CH_2)_n-NH_2$ under amines existence, such as mineral salt, such as potassium carbonate which acts as a base, and tertiary amine, react to the biphenyl alkyl bromide of a raw material [whether the alkylating agent which can manufacture the secondary amine object which is this invention compound, and is expressed with R12-E to a secondary amine object is made to react, and] The tertiary amine object which is this invention compound can be manufactured by making the amines expressed with $Y^1-(CH_2)_n-NHR^{12}$ react to the biphenyl alkyl bromide of a raw material. A reaction usually mixes an alkylating agent and an amine by arbitrary ratios among a suitable solvent, and is performed by stirring for 1 to 96 hours under cooling, a room temperature, or heating. The solvents which do not influence reactions, such as hydrocarbons, such as alcohols, such as a methanol and ethanol, benzene, and toluene, or THF, a dioxane, an acetonitrile, and DMF, DMSO, as a solvent, or those mixed solvents use, using organic tertiary amine, such as mineral salt, such as potassium carbonate and a sodium carbonate, and a triethylamine, a pyridine, as a base, and it is carried out by setting the ratio of an alkylating agent and an amine object to 1:10-10:1. The ratio of an alkylating agent and an amine object is preferably set to 1:5-1:1, and it is carried out under a room temperature or heating for 2 to 24 hours.

[0050] Moreover, the compound which has amide combination as X1 among the nitril objects which are precursors of this invention compound expressed with a formula (1) is compoundable with for example, the following reaction formula (b-1) or (b-2) the reaction shown.

[0051]

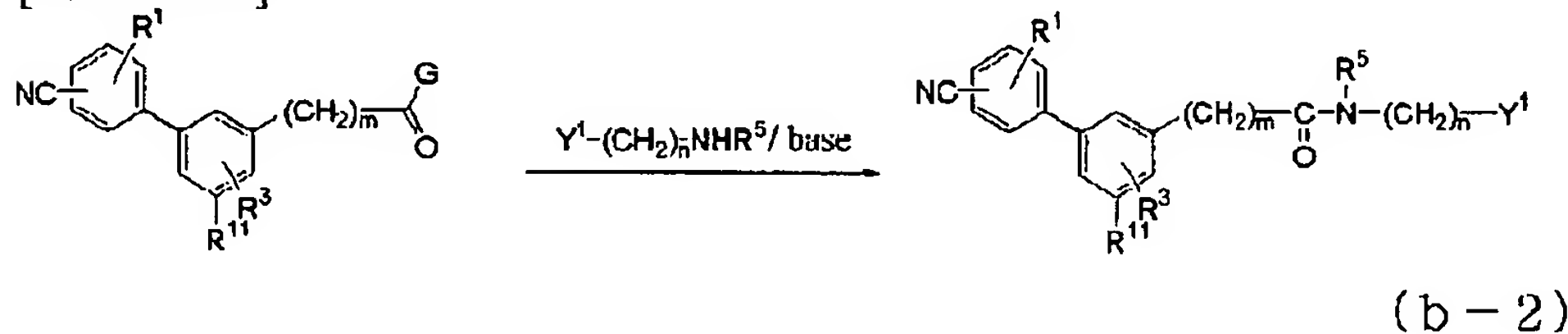
[Formula 11]



[0052] R^1 , R^3 , R^5 , Y^1 , m , and n are equal to the definition in a formula (1) among [reaction formula. The fluorine atom among the substituents R^2 as which R^{11} is defined by the formula (1), a chlorine atom, meaning a bromine atom, a hydroxyl group (or the protector), the amino group (or the protector), C1 - 10 alkoxy groups, and a methoxycarbonyl group, G means bases, such as a halogen, an acyloxy machine, p-nitroglycerine phenoxy machine, and a hydroxyl group]

[0053]

[Formula 12]



[0054] R^1 , R^3 , R^5 , Y^1 , m , and n are equal to the definition in a formula (1) among [reaction formula. The fluorine atom among the substituents R^2 as which R^{11} is defined by the formula (1), a chlorine atom, meaning a bromine atom, a hydroxyl group (or the protector), the amino group (or the protector), C1 - 10 alkoxy groups, and a methoxycarbonyl group, G means bases, such as a halogen, an acyloxy machine, p-nitroglycerine phenoxy machine, and a hydroxyl group]

[0055] the above-mentioned reaction formula (b-1) -- or (b-2) can perform a reaction by using the conditions of a well-known amidation reaction. Usually, the activity derivative and amine compound of a carboxylic acid can be mixed among a suitable solvent under existence of a base, and an amide object can be acquired by acylating. As the activity derivative of a carboxylic acid to be used Activity ester,

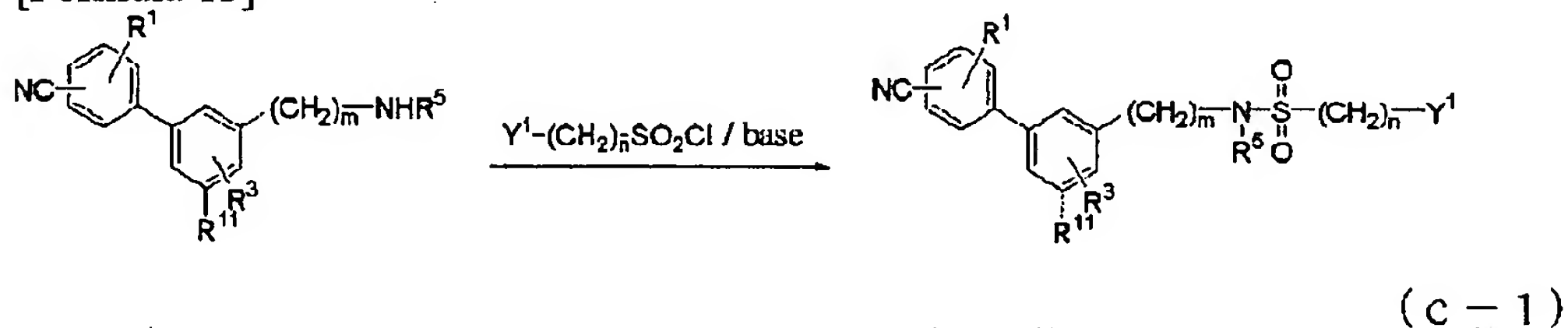
such as acid halide, a mixed acid anhydride, and p-nitrophenol, is used, and it is carried out to the bottom of cooling or a room temperature for 30 minutes to 24 hours. It is preferably carried out at 0-20 degrees C for 1 to 18 hours among solvents, such as aliphatic ether, such as halogenated hydrocarbons, such as a dichloromethane, and THF, diethylether, an acetonitrile, and DMF, or those mixed solvents, using tertiary amine, such as a triethylamine, as a base.

[0056] Moreover, such an amide object can be acquired also by the condensation reaction of amines and a carboxylic acid under condensing-agent existence, such as carbodiimides. In this case, as a solvent, halogenated hydrocarbons, such as DMF and chloroform, are suitable, and N and N-dicyclohexylcarbodiimide, a 1-ethyl-(3-(N and N-dimethylamino) propyl) carbodiimide, carbonyldiimidazole and a diphenyl phosphoryl azide, and a diethyl phosphoryl cyanide are suitable as a condensing agent. A reaction is usually performed under cooling or a room temperature for 2 to 48 hours.

[0057] Moreover, the compound which has sulfonamide structure as X1 among the nitril objects which are precursors of this invention compound expressed with a formula (1) is compoundable with for example, the following reaction formula (c-1) or (c-2) the reaction shown.

[0058]

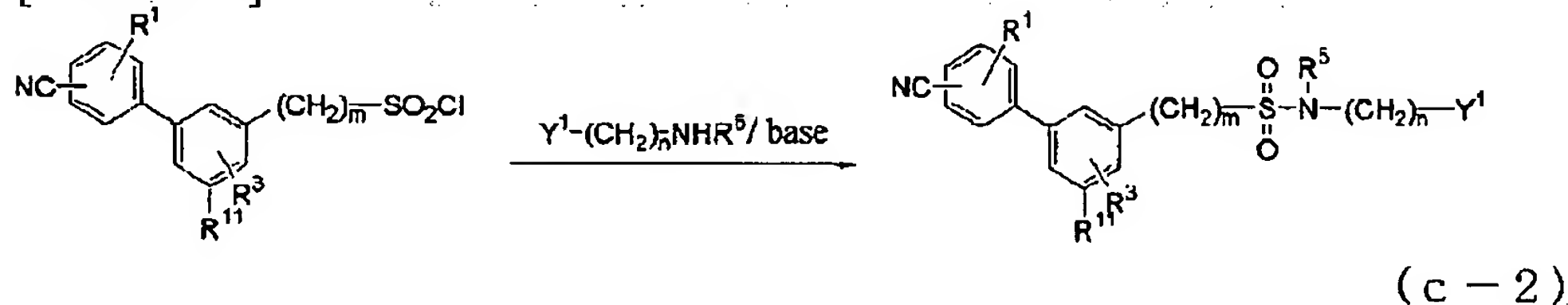
[Formula 13]



[0059] [reaction-formula Naka, and R1, R3, R5, Y1, m and n are equal to the definition in a formula (1), and R11 means a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group (or the protector), the amino group (or the protector), C1 - 10 alkoxy groups, and a methoxycarbonyl group among the substituents R2 defined by the formula (1).]

[0060]

[Formula 14]



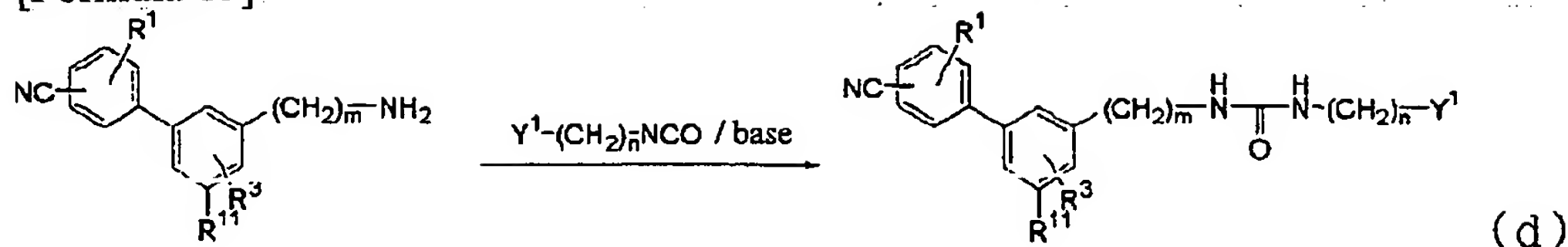
[0061] [reaction-formula Naka, and R1, R3, R5, Y1, m and n are equal to the definition in a formula (1), and R11 means a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group (or the protector), the amino group (or the protector), C1 - 10 alkoxy groups, and a methoxycarbonyl group among the substituents R2 defined by the formula (1).]

[0062] A reaction reaction formula (c-1) or (c-2) the reaction expressed is performed by making the activity derivative of an amine and a sulfonic acid react the bottom of existence of a base, and among a suitable solvent, and the target sulfonamide object can be acquired. As an activity derivative of a sulfonic acid, sulfonyl halide is suitable and is performed at 0-20 degrees C for 1 to 24 hours among solvents, such as aliphatic ether, such as halogenated hydrocarbons, such as a dichloromethane, and THF, diethylether, an acetonitrile, and DMF, or those mixed solvents, using tertiary amine, such as a triethylamine, as a base.

[0063] Moreover, the compound which has urea structure as X1 among the nitril objects which are precursors of this invention compound expressed with a formula (1) is compoundable with the reaction shown for example, by the following reaction formula (d).

[0064]

[Formula 15]



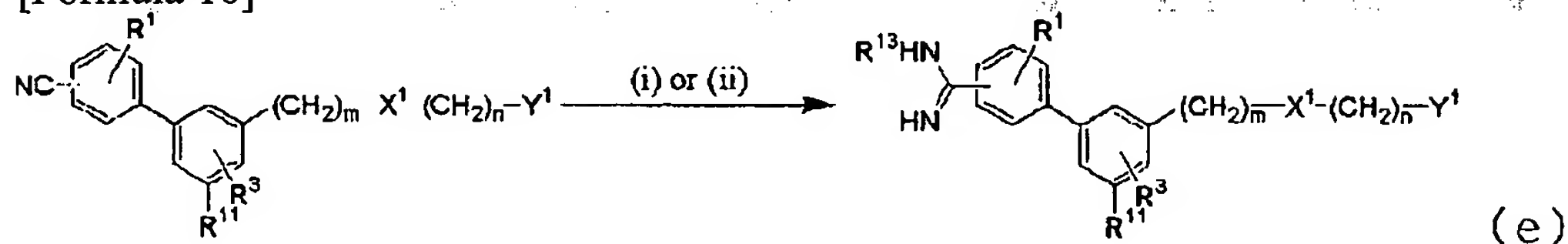
[0065] [reaction-formula Naka, and R1, R3, Y1, m and n are equal to the definition in a formula (1), and R11 means a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group (or the protector), the amino group (or the protector), C1 - 10 alkoxy groups, and a methoxycarbonyl group among the substituents R2 defined by the formula (1).]

[0066] That is, the compound which has urea structure as X1 can be manufactured by making the amine and isocyanate derivative of a raw material react under suitable cooling among a solvent, or heating. The solvents used at this reaction are DMF, THF, a dioxane, a dichloroethane, chloroform, an acetonitrile, DMSO, benzene, toluene, etc.

[0067] As mentioned above, the nitril object which is manufactured by the reaction shown by the above-mentioned reaction formula (a-1), (a-2), (b-1), (b-2), (c-1), (c-2), and (d) and which is a precursor of this invention compound is the following reaction formula (e).

[0068]

[Formula 16]



[0069] R1, R3, X1, Y1, m, and n are equal to the definition in a formula (1) among [reaction formula. The fluorine atom among the substituents R2 as which R11 is defined by the formula (1), a chlorine atom, meaning a bromine atom, a hydroxyl group (or the protector), the amino group (or the protector), C1 - 10 alkoxy groups, and a methoxycarbonyl group, R13 means a hydrogen atom, a hydroxyl group, the amino group, C1 - 10 alkyl groups, an aryl group, and an aralkyl machine] By being alike and giving an amidino-ized reaction as shown, it is convertible for the bends amidine derivative which is this invention compound. This amidino-ized reaction is performed by the reaction condition as shown in the following (i) or (ii).

[0070] (i) -- amidino-ized reaction: which passes through IMIDATO-ization using the alcoholic solution of a hydrogen halide -- the reaction which obtains IMIDATO from a nitril object and alcohols advances by dissolving in the alcohols of the carbon numbers 1-4 containing hydrogen halides, such as a hydrogen chloride and a hydrogen bromide, and agitating an alkoxy methylphenyl benzonitrile object A reaction is usually performed at -20-30 degrees C for 12 to 96 hours. It is preferably carried out at -10-+30 degrees C among the methanol of a hydrogen chloride, or an ethanol solution for 24 to 72 hours. The reaction of IMIDATO and ammonia advances by agitating IMIDATO in halogenated hydrocarbons, such as aliphatic ether, such as alcohols of the carbon numbers 1-4, such as a methanol containing ammonia, and ethanol, or diethylether, or a dichloromethane, and chloroform, or those mixed solvents, and the bends amidine derivative (1) which is this invention compound generates it. A reaction is usually performed at the temperature of -10-+50 degrees C for 1 to 48 hours. It is preferably carried out at 0-30 degrees C among a methanol or ethanol for 2 to 12 hours.

[0071] (ii) -- amidino-ized reaction: which passes through IMIDATO which adjusted the hydrogen halide with the entrainment directly -- the reaction of a nitril object and alcohol A nitril object For example, aliphatic ether, such as diethylether, Or, dissolving in aprotic solvents, such as halogenated hydrocarbons, such as chloroform, or benzene, and adding and agitating the alcohols of the equivalent or

the superfluous carbon numbers 1-4 - Blow the hydrogen-halide of a hydrogen chloride or a hydrogen bromide at 30-0 degree C for 30 minutes to 6 hours, stop an entrainment after that, and go on by agitating at 0-50 degrees C for 3 to 96 hours. Agitating among the halogenated hydrocarbons containing the equivalent, a superfluous methanol, or ethanol preferably, in -10-0 degree C, a hydrogen chloride is blown for 1 to 3 hours, an entrainment is stopped after that, and it agitates at 10-40 degrees C for 8 to 24 hours. Thus, obtained IMIDATO is convertible for the bends amidine derivative (1) which is this invention compound by agitating in halogenated-hydrocarbon solvents, such as aliphatic ether solvents, such as an alcoholic solvent of the carbon numbers 1-4, such as a methanol containing ammonia, and ethanol, or diethylether, or chloroform, or those mixed solvents. A reaction is usually performed at the temperature of -20-+50 degrees C for 1 to 48 hours. It is preferably carried out at 0-30 degrees C among saturated-ammonia ethanol for 2 to 12 hours.

[0072] Moreover, it is manufactured by the ester hydrolysis of the compound which has a methoxycarbonyl group as R9 among the bends amidine compounds manufactured by the above-mentioned reaction formula (e) about the compound which has a carboxyl group as R2 among the compounds shown by the formula (1). This adding-water decomposition reaction can be performed to the bottom of a basic condition, an acid condition, or neutrality condition if needed. At the reaction under basic conditions, a sodium hydroxide, a potassium hydroxide, a lithium hydroxide, a barium hydroxide, etc. are mentioned as a base to be used, Lewis acids, such as a hydrochloric acid, a sulfuric acid, and boron trichloride, a trifluoroacetic acid, p-toluenesulfonic acid, etc. are mentioned under acid conditions, and enzymes, such as halogen ion, such as an iodation lithium and a lithium bromide, a thiol or an alkali-metal salt of SERENORU, an iodine trimethyl silane, or esterase, are mentioned under neutrality condition. As a solvent used for a reaction, polar solvents, such as water, alcohol, an acetone, a dioxane, and THF, DMF, DMSO, or those mixed solvents are used. a reaction -- usually -- a room temperature or warming -- it carries out in the bottom for 2 to 96 hours Suitable conditions, such as reaction temperature and reaction time, change with reaction conditions to be used, are suitably chosen by the conventional method, and are performed.

[0073] Thus, about the obtained compound which has a carboxyl group as a substituent R2, a carboxyl group is convertible for other ester objects by the method shown in following (iii), (iv), and (v).

[0074] Conversion to the alkoxy carbonyl group of a carboxyl group : The compound which has a carboxyl group as a substituent R2 among the compounds expressed with a formula (4), (iii) the equivalent or a superfluous alkylating agent (for example, an acetoxy methyl chloride --) Acyloxy methyl chlorides or allyl chlorides, such as a PIBARO yloxy methyl chloride, Benzyl chlorides Or the inside of non-proton nature polar solvents, such as aliphatic ether, such as halogenated hydrocarbons, such as a dichloromethane, or THF, or DMF, or those mixed solvents, In -10-+80 degrees C, a carboxyl group is convertible for an alkoxy carbonyl group by making it react for 1 to 48 hours under tertiary amine existence, such as a triethylamine and a diisopropyl ethylamine. Preferably, it is carried out at 20-60 degrees C under diisopropyl ethylamine existence for 2 to 24 hours using an alkylating agent with superfluous equivalent - smallness.

[0075] (iv) -- conversion [to the aralkoxy carbonyl machine of a carboxyl group]: -- if the compound which has a carboxyl group as a substituent R2 among the compounds expressed with a formula (4), and alcohols, such as the equivalent or superfluous benzyl alcohol, are made to react under acid-catalyst existence, such as a hydrogen chloride, a sulfuric acid, and a sulfonic acid, by using halogenated hydrocarbons, such as a dichloromethane, as a solvent, a carboxyl group is convertible for an aralkoxy carbonyl machine. A reaction is usually performed under a room temperature or heating for 1 to 72 hours. Preferably, it is carried out at 20-60 degrees C under diisopropyl ethylamine existence for 2 to 24 hours using alcohols with superfluous equivalent - smallness.

[0076] (v) -- conversion [to the aryloxy carbonyl group of a carboxyl group]: -- if the compound which has a carboxyl group as a substituent R2 among the compounds expressed with a formula (4), and the aromatic compound which has hydroxyl groups, such as the equivalent or a superfluous phenol, are made to react under condensing-agent existence, such as a dicyclohexylcarbodiimide, by using aliphatic ether, such as diethylether, as a solvent, a carboxyl group is convertible for an aryloxy carbonyl group A

reaction is usually performed at degree C 0 to 50 degrees for 1 to 48 hours. Preferably, it is carried out at a room temperature for 3 to 24 hours.

[0077] Moreover, the compound which has a carboxyl group as R₂ makes acid halide the well-known technique, for example, a carboxyl group, by oxalyl chloride etc., is making aqueous ammonia react and can also change it into a carbamoyl group. By making it react with acid halide and an N-methyl-N-methoxy amine similarly, it is convertible for an N-methyl-N-methoxy carbamoyl group, and this reacts with further various alkyl magnesium reaction agents, and can be changed into an alkyl carbonyl group.

[0078] In addition, in addition to this, the compound shown by the formula (1) can be manufactured by combining arbitrarily processes which this contractor can usually adopt, such as well-known etherification, amidino-izing, hydrolysis, formation of alkyl imidoyl, amidation, and esterification.

[0079] The well-known method, for example, extraction, precipitation, a fractionation chromatography, fractional-crystallization-izing, recrystallization, etc. can isolate and refine the alkoxy methylphenyl bends amidine derivative I manufactured as mentioned above. Moreover, the salt of this invention compound permitted pharmacologically can be manufactured by giving the usual salt formation reaction.

[0080] There is an effect which suppresses FXa activity and the biphenyl amidine derivative of this invention or its salt permitted pharmacologically can be used as a FXa inhibitor as the preventive in which clinical application is possible, and/or a treatment agent to thrombus plug nature disorders, such as myocardial infarction, cerebral thrombosis, deletion artery thrombosis, and deep venous thrombosis.

[0081] Moreover, the biphenyl amidine derivative of this invention can be used as the physic constituent which consists of support permitted pharmaceutically, can cast this physic constituent to various pharmaceutical forms, and can prescribe it for the patient by taking orally or the parenteral. As parenteral administration, medication into a vein, hypodermically, muscles, transderma, the rectum, pernasality, and instillation is mentioned, for example.

[0082] The following is mentioned as a pharmaceutical form of this physic constituent. For example, in the case of an internal use agent, pharmaceutical forms, such as a tablet, the pilule, a granule, powder, solution, suspension, syrup, and a capsule, are mentioned.

[0083] Here, as the molding method of a tablet, it can cast by the usual method using support permitted pharmaceutically, such as an excipient, a binder, and disintegrator. The pilule, a granule, and powder as well as the case of a tablet can be cast by the usual method using an excipient etc. The molding method of solution, the suspension, and the syrup can be cast by the usual method using glycerol esters, alcohols, water, vegetable oil, etc. The molding method of a capsule can cast a granule, powder, or solution by filling up capsules, such as gelatin.

[0084] In the case of a vein, hypodermically, and intramuscular administration, a medicine can be prescribed for the patient as injection among parenteral administration agents. The case where a biphenyl amidine derivative is dissolved in the un-water-soluble solution which consists of organic ester, such as a propylene glycol, a polyethylene glycol, and vegetable oil, as injection when dissolving in water-soluble solution, such as a physiological saline, etc. is mentioned.

[0085] In the case of dermal administration, it can use as pharmaceutical forms, such as an ointment and cream pharmaceuticals. An ointment is mixed with fats and oils, vaseline, etc., a biphenyl amidine derivative is used for it, it can mix with an emulsifier and cream pharmaceuticals can cast a biphenyl amidine derivative.

[0086] In rectum medication, it can consider as a suppository using a gelatin soft capsule etc.

[0087] In pernasal medication, it can use as a tablet which consists of a liquefied or powdered constituent. As a basis of a liquefied agent, water, brine, a phosphate buffer solution, the acetic-acid buffer solution, etc. are used, and a surfactant, the antioxidant, the stabilizer, the preservative, and the viscous grant agent may be included further. As a basis of a powdered agent, for example, damage-at-sea solubility things, such as for example, the thing of water absorptivity, such as polyacrylates of water-solubility, cellulose low-grade alkyl ether, a polyethylene-glycol polyvinyl pyrrolidone, an amylose, and a pullulan, or celluloses, starch, proteins, gums, and bridge formation vinyl polymerization objects, are mentioned, and the thing of water absorptivity is desirable. Moreover, you may mix and use these.

Furthermore to a powdered agent, you may add an antioxidant, a coloring agent, a preservative, antiseptics, a **** agent, etc. This liquefied agent and a powdered agent can be prescribed for the patient for example, using a spray instrument etc.

[0088] In the medication in applying eyewash, it can be used as a water or non-water applying-eyewash agent. A sterilized pure water, a physiological saline, etc. can be used for a solvent as a water applying-eyewash agent. When only a sterilized pure water is used as a solvent, suspension, such as a surfactant and a macromolecule thickener, can be added and it can use as aqueous suspension eye lotions, and solubilizing agents, such as a nonionic surfactant, can be added and it can also use as solubilization eye lotions. As non-aqueous ophthalmic solution, the non-aqueous solvent for injection can be used for a solvent, and it can use as non-aqueous suspension eye lotions.

[0089] When medicating an eye by methods other than the ophthalmic solution, it can consider [*****] as pharmaceutical forms, such as ophthalmic ointment, application solution, epipastic, and an insertion agent.

[0090] Moreover, when inhaling from a nose, a mouth, etc., it is inhaled, using for example, the aerosol spray for inhalation etc. as the solution or suspension of a biphenyl amidine derivative and the medicine manufacture excipient generally used. moreover, dryness -- the biphenyl amidine derivative made powdered can be prescribed for the patient using the inhalator contacted lungs and directly

[0091] In a tablet various [these], pharmaceutical support permitted, such as an isotonizing agent, a preservative, antiseptics, a wetting agent, a buffer, an emulsifier, a dispersant, and a stabilizer, can be added if needed.

[0092] Moreover, if needed, it can deal with combination of a germicide, the filtration using the bacterium hold filter, heating, irradiation, etc. for a tablet various [these], and can be made sterile to it. Or a sterile solid tablet is manufactured, and it can also be used for a sterile solution suitable just before use, dissolving or suspending.

[0093] Although the dose of the biphenyl amidine derivative of this invention changes with the kind of disorder, a route of administration, a patient's symptom, age, sex, weights, etc., generally, in internal use, it is about a 1-500mg/day/person and is a 10-300mg/day/person preferably. In parenteral administration, such as a vein, hypodermically, muscles, transderma, the rectum, pernasality, instillation, and inhalation, it is about a 0.1-100mg/day/person and is a 0.3-30mg/day/person preferably.

[0094] Moreover, when using the biphenyl amidine derivative of this invention as a preventive, according to each symptom, a medicine can be beforehand prescribed for the patient according to a well-known method.

[Translation done.]

EXAMPLE 5

JP 2000-178243

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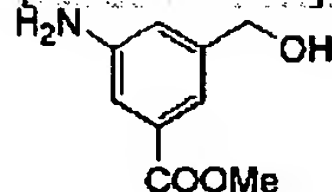
EXAMPLE

[Example] The example of manufacture, an example, and the example of an examination explain this invention concretely below. However, the range of this invention is not restricted by these examples in any meanings.

[0096] [The example 1 of manufacture]

3-amino-5-hydroxymethyl benzoic-acid methyl ester [0097]

[Formula 17]



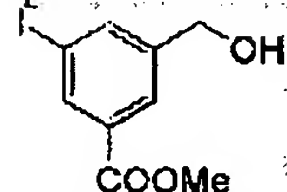
[0098] 43.4ml of borane dimethyl sulfide complexes was added having melted 85g of 3-nitroglycerine-5-methoxycarbonyl benzoic acids to THF200ml under the nitrogen air current, and carrying out ice-cooling stirring. After stirring for 18 hours, 200ml water was added and 96g of potassium carbonate was added. Ethyl acetate extracted and brine washed the organic layer. After drying with magnesium sulfate, the obtained solid-state was melted to 800ml of ethyl acetate, 10%Pd/C750mg was added, and it stirred under the hydrogen air current. After the reaction end, after performing filtration, filtrate was condensed, and 64g of compounds of a title was obtained.

¹H-NMR(270MHz, CDCl₃): delta 2.30 (s, 1H), 3.89 (s, 3H), 4.64 (s, 1H), 6.89 (s, 1H), 7.26 (s, 1H), 7.39 (s, 1H)

[0099] [The example 2 of manufacture]

5-hydroxymethyl-3-iodine benzoic-acid methyl ester [0100]

[Formula 18]



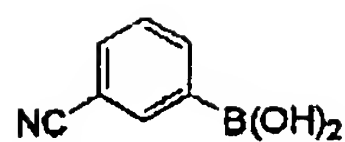
[0101] 75g of hydroiodic acids was added having melted 34.3g of compounds obtained in the example 1 of manufacture to THF200ml, and carrying out ice-cooling stirring. 100ml solution of 13.73g of sodium nitrites was added stirring. After stirring for 40 minutes at 0 degree C, 150ml solution of 34.6g of potassium iodide was added. After stirring at 40 degrees C for 2 hours, 300ml water was added and condensed. Ethyl acetate extracted and brine washed the organic layer. After drying by the sodium sulfate, the silica gel column chromatography refined and 23.1g (42%) of compounds of a title was obtained.

¹H-NMR(270MHz, CDCl₃): delta 1.81 (t, 1H, J= 5.6Hz), 3.92 (s, 3H), 4.72 (d, 1H, J= 5.6Hz), 7.93 (s, 1H), 7.98 (s, 1H), 8.29 (s, 1H)

[0102] [The example 3 of manufacture]

Dihydroxy-(3-cyano phenyl) borane [0103]

[Formula 19]



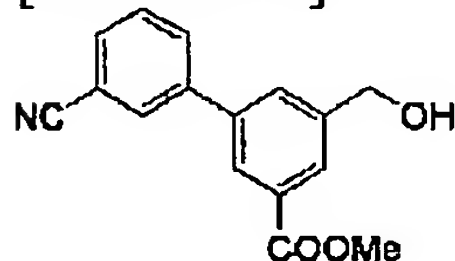
[0104] 3-bromobenzo nitril 20g was melted to dryness THF100ml, and tri-isopropoxyborane 37.6ml was added under nitrogen-gas-atmosphere mind. 98.3ml of 1.6Mn-butyl-lithium hexane solutions was dropped in about 30 minutes, cooling and agitating this solution at -78 degrees C. After agitating at a room temperature for 30 minutes, it cooled at 0 degree C and 220ml of 4M sulfuric acids was added. This solution was again cooled at 0 degree C overnight, after carrying out a heating rotary flow, 340ml of 5M sodium-hydroxide solution was added, and it extracted by diethylether 200ml. The water layer was divided, and 6M hydrochloric acid was added until it was set to pH 2. 300ml of ethyl acetate extracted twice, and the solvent was distilled off after drying with magnesium sulfate. The obtained rough product was *****ed from DMF-water and 11.6g (72%) of compounds of a title was obtained as a needlelike light yellow crystal.

¹H-NMR(270MHz, DMSO-d₆):delta7.6- 8.3 (m, 4H) and 8.5 (brs, 2H)

[0105] [The example 4 of manufacture]

3-(3-cyano phenyl)-5-(hydroxymethyl) benzoic-acid methyl ester [0106]

[Formula 20]



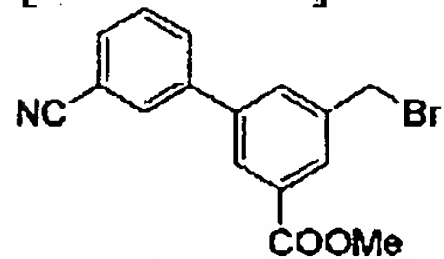
[0107] 2.32g [of compounds], 2.18g [of potassium carbonate], and tetrakis (triphenylphosphine) palladium 456mg which dissolved in dryness DMF50ml under the nitrogen air current, and obtained 3.08g of compounds obtained in the example 2 of manufacture in the example 3 of manufacture in this solution was added, and heating churning was carried out at 90 degrees C overnight. Water was added, the reaction was stopped, ethyl acetate extracted, and the solvent was distilled off after drying with magnesium sulfate. The silica gel column chromatography refined and the compound of a title was obtained as 2.05g (73%) and a colorless crystal.

¹ H-NMR(270MHz, CDCl₃): delta2.1 (brs, 1H), 3.96 (s, 3H), 4.84 (d, 2H, J= 3.7Hz), 7.5-8.2 (m, 7H)

[0108] [The example 5 of manufacture]

3-(3-cyano phenyl)-5-(bromomethyl) benzoic-acid methyl ester [0109]

[Formula 21]



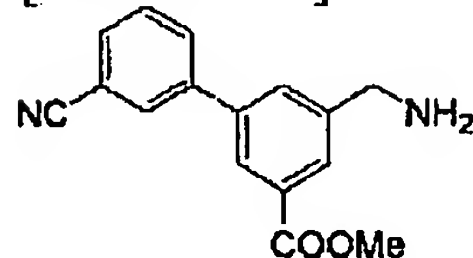
[0110] After adding diethylether 20ml to 1.0g of compounds obtained in the example 4 of manufacture and considering as suspension, 0.5ml of phosphorus tribromide was dropped slowly. After stirring reaction mixture under a room temperature for 19 hours, it extracted. After saturation brine's having washed the organic layer and drying by the sodium sulfate Distilling off of the bottom solvent of reduced pressure obtained the compound of a title as a solid-state of light yellow (1.2g, 98%).

¹ H-NMR(270MHz, CDCl₃): delta3.97 (s, 3H), 4.58 (s, 2H), 7.5-7.9 (m, 5H), 8.1-8.2 (m, 2H)

[0111] [The example 6 of manufacture]

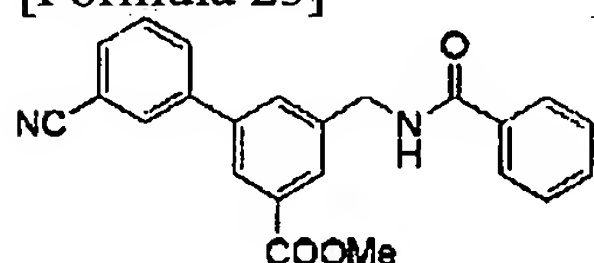
3-(3-cyano phenyl)-5-(aminomethyl) benzoic-acid methyl ester [0112]

[Formula 22]



[0113] 3-(3-cyano phenyl)-5-(bromomethyl) benzoic-acid methyl-ester 1.1g obtained in the example 5 of manufacture was melted to DMF 33ml, and 325mg of sodium azides was added slowly. After stirring reaction mixture under a room temperature for 2 hours, water 80mL and ethyl-acetate 120mL were added, the organic substance was extracted, and the water layer was extracted twice in ethyl-acetate 100mL. Saturation brine washed the extract, the bottom solvent of reduced pressure was distilled off after dryness in anhydrous-sodium-sulfate solution, and the light yellow oil-like 3-(3-cyano phenyl)-5-(azide methyl) benzoic-acid methyl ester was obtained as a rough product. In this way, after having put the obtained 3-(3-cyano phenyl)-5-(azide methyl) benzoic-acid methyl ester into the flask, making it dissolve in ethanol 66mL and adding 1.1g of palladium-barium carbonates, the inside of a flask was replaced from hydrogen. After having stirred at the room temperature as it is for 6 hours, carrying out cerite filtration of the catalyst and condensing a filtrate, the silica gel column chromatography refined and 794mg of specified substance of a title was obtained (90% of two steps of yield). GC-MS(M-H) = 265 [0114] [The example 7 of manufacture]

3-(3-cyano phenyl)-5-benzoyl aminomethyl benzoic-acid methyl ester [0115]
[Formula 23]



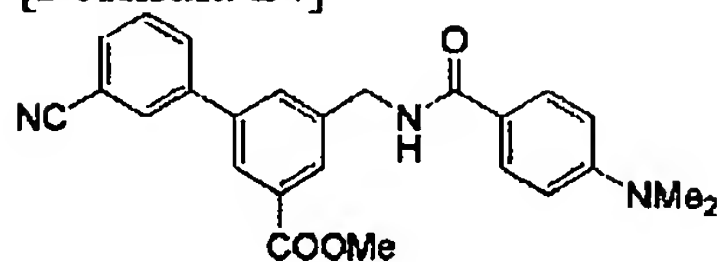
[0116] 100mg of compounds obtained in the example 6 of manufacture was dissolved in chloroform 0.7mL. while adding and stirring 0.3M chloroform solution 1.5mL of benzoin chloride in this solution -- the 0.3M chloroform solution of a triethylamine -- in addition, it stirred at the room temperature for 2.5 hours. Aminomethyl resin (1.04 mmol/g) 200mg was put into reaction mixture, it stirred at the room temperature for 12 hours, reaction mixture was filtered with the glass filter, saturation sodium-hydrogencarbonate solution 1mL was added to the filtrate, liquids were separated, the extract was condensed and the specified substance was obtained. 115mg, 84% of yield.
MS=371.0(M+H)

By this technique, the nitril object which is a precursor of the examples 1, 2, 3, 4, 5, 15, 16, 17, and 18 of manufacture shown in Table 1 and Table 2 was acquired.

[0117] [The example 8 of manufacture]

3-(3-cyano phenyl)-5-(4-N and N-dimethylamino phenyl carbonyl) aminomethyl benzoic-acid methyl ester [0118]

[Formula 24]



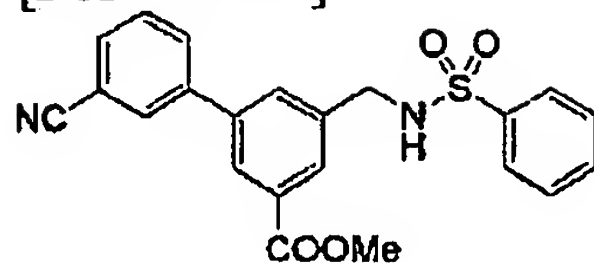
[0119] 27mg of compounds obtained in the example 6 of manufacture was dissolved in chloroform 2.0mL. 21mg of 4-N and N-dimethylamino benzoic acids was added, HOBt 27mg and 48mg of EDCI hydrochlorides were added further, and it agitated at the room temperature all night. reaction mixture -- the product made from Varian -- the anion-exchange-resin column SAX for cation-exchange-resin column SCX row solid phase extraction for solid phase extraction was presented, and 2 convention ammonia methanol solution extracted the specified substance by which SCX was adsorbed except for the impurity. The extract was condensed and 50mg of compounds of a title was obtained quantitatively.

MS(M+H) = 414.0 -- by this technique, the nitril object which is a precursor of the examples 6, 7, 8, 9, 10, 11, 12, 13, 14, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, and 32 of manufacture was acquired

[0120] [The example 9 of manufacture]

3-(3-cyano phenyl)-5-benzenesulphonyl aminomethyl benzoic-acid methyl ester [0121]

[Formula 25]



[0122] 27mg of compounds obtained in the example 6 of manufacture was dissolved in chloroform 0.5mL. while adding and stirring 0.2M chloroform solution 0.6mL of benzenesulfonic-acid chloride in this solution -- 0.2M chloroform solution 0.6mL of a triethylamine -- in addition, it stirred at the room temperature for 12 hours Aminomethyl resin (1.04 mmol/g) 200mg was put into reaction mixture, it stirred at the room temperature for 12 hours, reaction mixture was filtered with the glass filter, saturation sodium-hydrogencarbonate solution 1mL was added to the filtrate, liquids were separated, the extract was condensed and the specified substance was obtained quantitatively. 42mg.

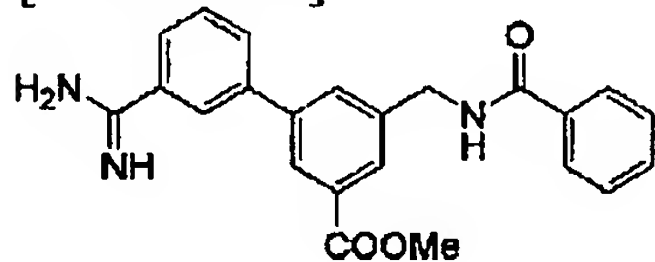
MS=371.0(M+H)

By this technique, the nitril object which is a precursor of the examples 33, 34, and 35 shown in Table 2 was acquired. Moreover, the nitril object which is a precursor of the examples 36, 37, and 38 of manufacture shown in Table 5 was acquired by using an isocyanate derivative for a raw material instead of a sulfonic-acid chloride derivative, and performing same operation.

[0123] [Example 1]

3-(3-amidino phenyl)-5-benzoyl aminomethyl-methyl benzoate [0124]

[Formula 26]



[0125] 38mg of compounds of the example 7 of manufacture was dissolved in dichloromethane 60ml, and methanol 3.0ml was added. Hydrogen chloride gas was blown for 30 minutes, carrying out ice-cooling stirring. After stirring at a room temperature for 30 minutes by 0 degree C for 20 hours, concentration hardening by drying was carried out. 30ml of saturated-ammonia-ethanol solutions was added, and it condensed, after stirring at a room temperature for 5 hours. Preparative isolation refining was performed for the obtained rough product using HPLC (ODS, elution solvent:water-methanol), and 24mg of specified substance of a title was obtained. 60%.

MS=388.2(M+H)

Same technique The examples 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, and 37 of manufacture shown in Table 1, Table 2, Table 3, Table 4, and Table 5, The compound of 38 was compounded.

[0126] [Example 2]

The measurement sample of the Xth factor (FXa) inhibitory action of activation blood coagulation was dissolved in the water which added the organic solvent (DMSO, ethanol, or methanol) of water or suitable concentration, and it considered as the sample. After adding 100mM tris-buffers (pH 8.4) 90microl, 50 mU/ml man FXa50mM tris-buffers (pH 8.4) solution 20microl, and 2mM substrate (the first chemistry S-2765) in 70micro of samples 1 which carried out stage dilution with water and incubating for 30 minutes, 50micro of acetic acids 1 was added 50%, and the absorbance (A405) was measured. What added tris buffers instead of FXa was made blank, and what added water instead of the sample was considered as control. It asked for prevention activity (IC50) 50%, and considered as the index of FXa inhibitory action. Consequently, the prevention activity of 50= 1-10micro [of ICs] M was accepted at the compound of the examples 4, 5, 7, 8, 17, 18, and 19 of manufacture to the compound of IC50=0.1-1microM and the examples 1, 6, 15, 16, 21, 22, and 29 of manufacture, and it became clear that the biphenyl amidine compound by this invention is Xa inhibitor.

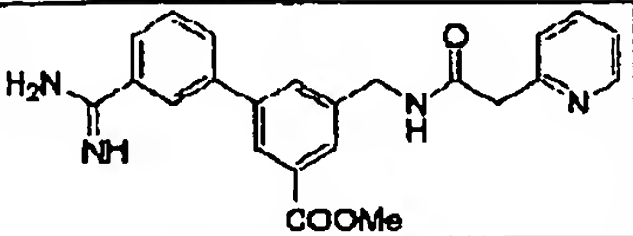
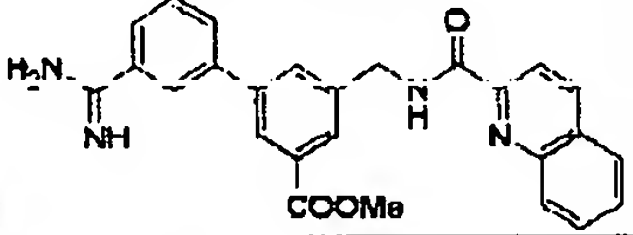
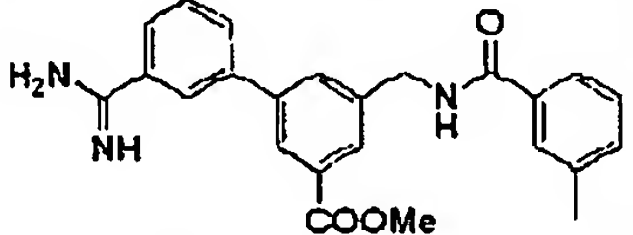
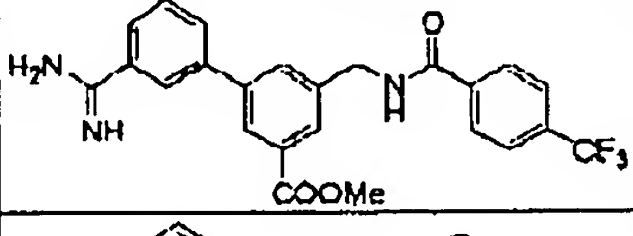
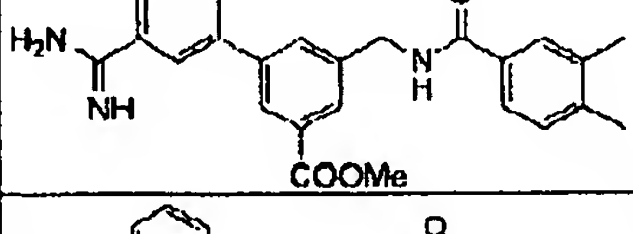
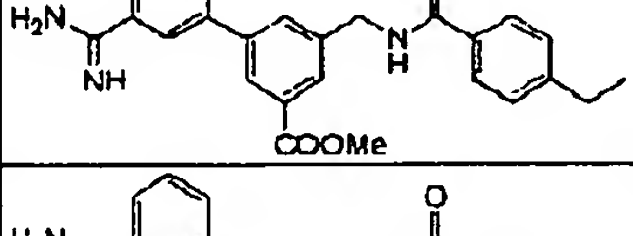
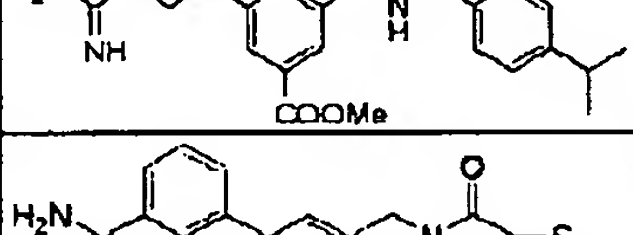
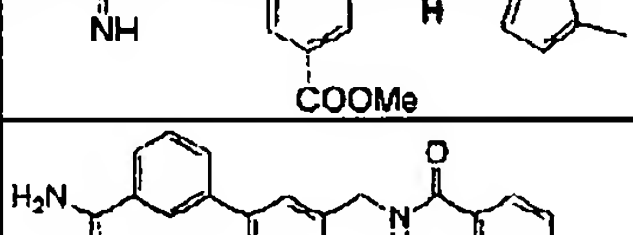
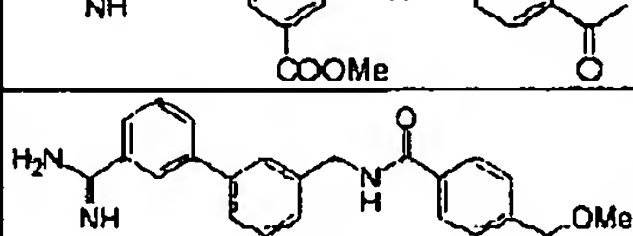
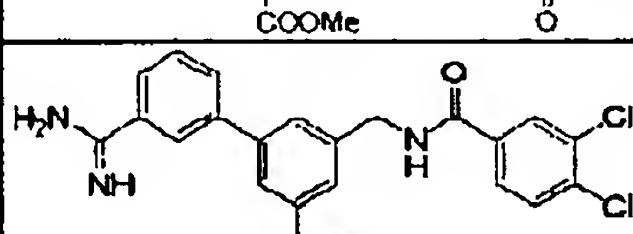
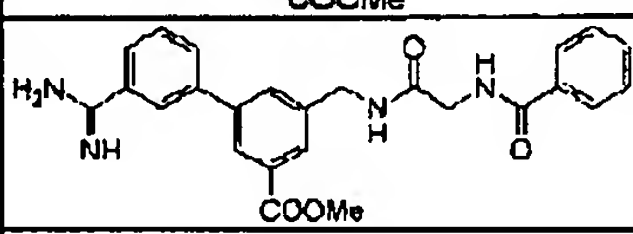
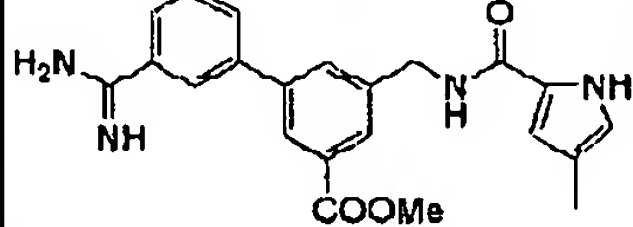

[0127]

[Table 1]

製造例	構造	MSデータ
1		388.2 [M+H]
2		389.0 [M+H]
3		402.0 [M+H]
4		402.4 [M+H]
5		418.2 [M+H]
6		403.2 [M+H]
7		417.2 [M+H]
8		431.2 [M+H]
9		404.2 [M+H]
10		404.2 [M+H]
11		403.2 [M+H]
12		403.2 [M+H]

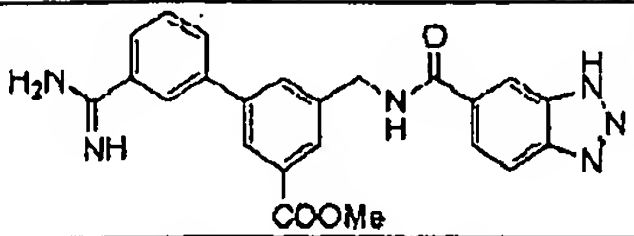
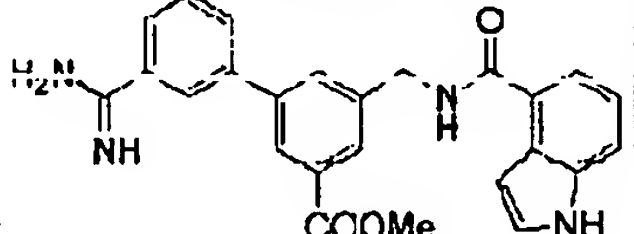
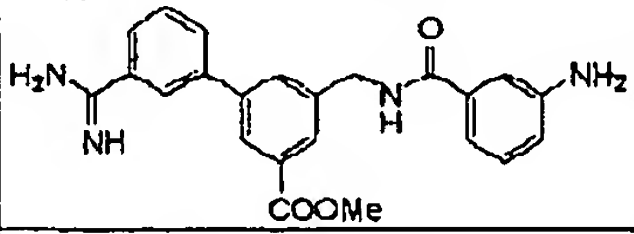
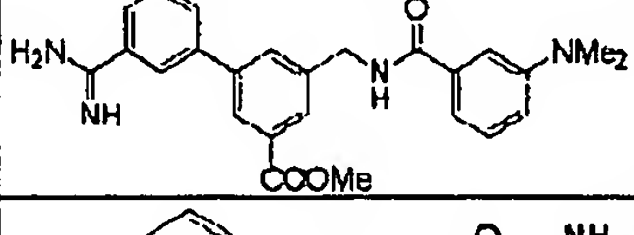
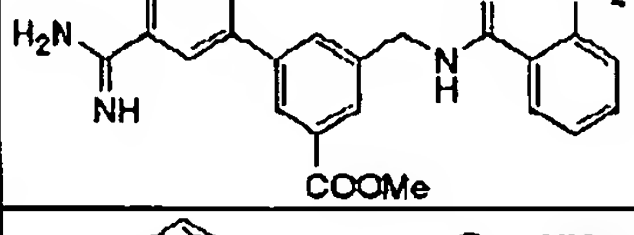
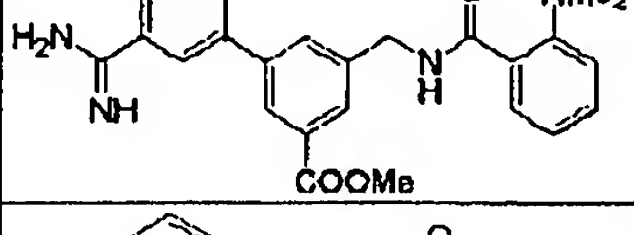
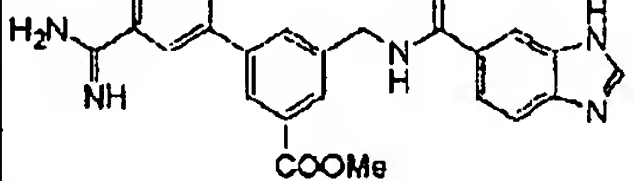
[0128]

[Table 2]

13		403.2 [M+H]
14		439.2 [M+H]
15		402.2 [M+H]
16		456.2 [M+H]
17		416.2 [M+H]
18		416.2 [M+H]
19		430.2 [M+H]
20		408.2 [M+H]
21		430.2 [M+H]
22		446.2 [M+H]
23		456.0 [M+H]
24		445.0 [M+H]
25		391.2 [M+H]

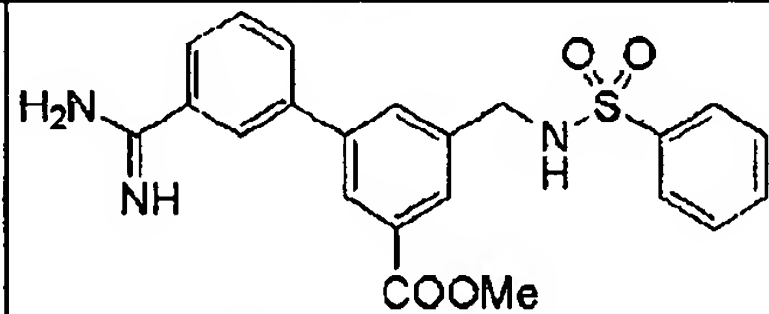
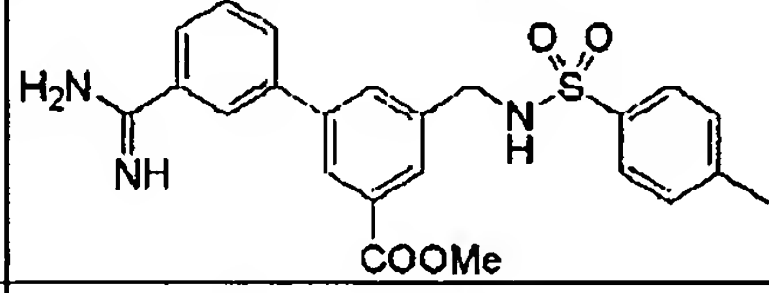
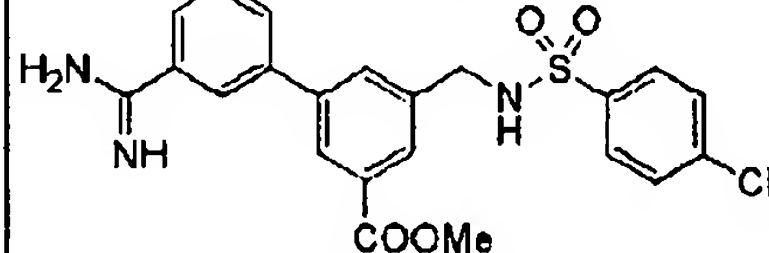
[0129]

[Table 3]

26		429.4 [M+H]
27		427.2 [M+H]
28		403.4 [M+H]
29		431.2 [M+H]
30		403.4 [M+H]
31		431.4 [M+H]
32		423.2 [M+H]

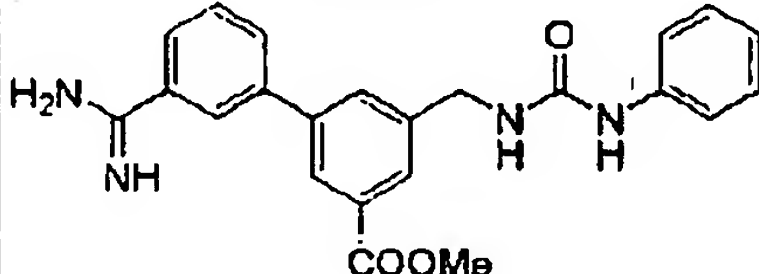
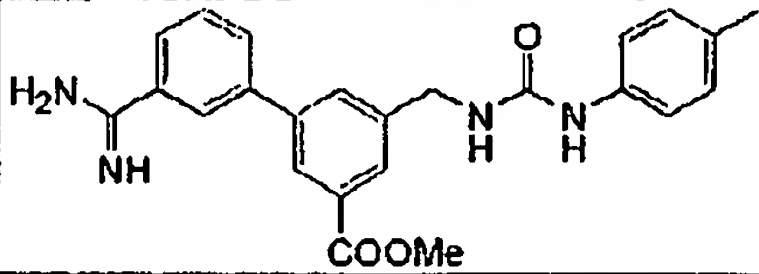
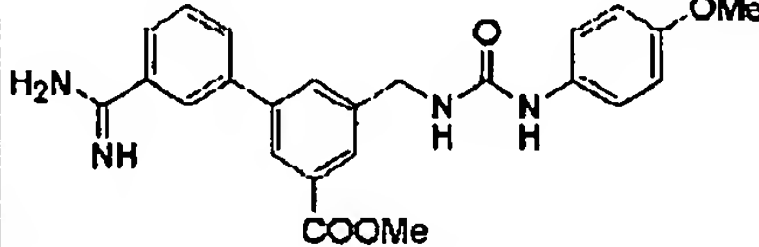
[0130]

[Table 4]

製造例	構造	MSデータ
33		24.0 [M+H]
34		438.0 [M+H]
35		453.2 [M+H]

[0131]

[Table 5]

製造例	構造	MSデータ
36		403.0 [M+H]
37		417.0 [M+H]
38		433.0 [M+H]

[Translation done.]